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1862-1942

IN MEMORIAM

REUBEN PETERSON
1862-1942

R EUBEN PETERSON died at Duxbury, Massachusetts, on November 25, 1942, at the age of eighty. His death came rather unexpectedly after an illness of two months.

He was a direct descendant of George Soule, one of the Mayflower Pilgrims. He was educated at Harvard University, and after receiving his medical degree in 1889 he practiced in Grand Rapids, Michigan, for eight years. From 1898 to 1901 he was Professor of Gynecology at the Post Graduate Medical School of Chicago, and Assistant Professor of Obstetrics and Gynecology at Rush Medical School.

His period of service at the University of Michigan as Head of Obstetrics and Gynecology lasted thirty years, 1901 to 1931. It was here that he became famous as a teacher and developed the department into an excellent University Teaching Clinic. His proudest accomplishment was the organization of a system for the training of assistants. Strange indeed, in so doing he encountered actual opposition and criticism from heads of other departments. He was proud to have one of his own trained associates succeed him upon his retirement.

Dr. Peterson was chiefly a clinician. This no doubt was due to the period in which he studied and practiced. As laboratory methods developed he always eagerly embraced each new idea. But to him the laboratory was always an adjunct to his clinical work. He believed obstetrics and gynecology were inseparable and he taught and practiced both. He made many contributions to literature. The *Index Medicus* and the *Cumulative Index* recorded 219.

Dr. Peterson was greatly respected by his associates for the brilliancy of his work, his masterful ability to organize, and for his clear-cut teaching clinics. He was deeply loved for his homely virtues. Simplicity, honesty, kindness, and generosity were his outstanding traits.

He was beloved by all the medical students. His lectures were always interesting, well delivered and well organized, and sprinkled with many of the anecdotes for which he was so famous.

He received abundant recognition for his professional accomplishments. He was secretary and also chairman of the Section on Obstetrics and Gynecology and Abdominal Surgery of the American Medical Association, a founder of the American College of Surgeons, and was certified by the American Board of Obstetrics and Gynecology. In 1897 he was elected to membership in the American Gynecological Society and served as its President in 1911. He was a member of the Advisory Editorial Board of the *American Journal of Obstetrics and Gynecology* from the year of its founding until he retired from professional work. During this period he maintained a constant interest in the publication and nominated his successor at the University of Michigan, Dr. Norman Miller, to take his place on the Board. He was a member of numerous medical societies. During World War I he was a Major in the Medical Corps of the United States Army and had charge of medical recruiting in Michigan. In 1936 the University of Michigan granted him the honorary degree of Doctor of Science.

In 1889, immediately after graduation in medicine, Dr. Peterson married Miss Josephine Davis. Four children were born to them.

His was a rich life, full of accomplishments, and well lived. His memory will be a constant inspiration. We, his associates, with his many friends, will miss him.

George Kamperman.

Original Communications

ILIAC LYMPHADENECTOMY FOR GROUP II CANCER OF THE CERVIX*

Technique and Five-Year Results in 175 Cases

FRED J. TAUSSIG, M.D., ST. LOUIS, MO.

(From the Barnard Free Skin and Cancer Hospital)

THE logic of removing the important tributary lymph glands in cancer of the uterine cervix lies in the fact that radiation therapy, which is effective in eradicating the primary site of certain forms of cancer, fails except in few cases permanently to destroy cancer metastases in the lymph glands. In cancer of the breast, the oral cavity, the vulva, and the penis, lymph gland resections have for a long time been accepted as the standard treatment, associated with surgical ablation or radiation of the primary tumor. In cervix cancer, gland removal was for many years considered an essential feature of the radical Wertheim hysterectomy. The high primary operative mortality of this extensive procedure led many to abandon the gland resection and at present only a few surgeons, like Bonney in London, still adhere to this plan of treatment. Furthermore it is applicable only to the relatively small number of Group I (League of Nations Classification) cancers of the cervix. Group II cases, in which there is involvement of the parametrium or upper third of the vagina, without extension to the pelvic wall, are at least two to three times as numerous as the Group I cases. It was in this group that it seemed to me possible to obtain better results by combining lymphadenectomy with radiation of the primary tumor.

In 1930, Leveuf in France, and I independently conceived the possibility of this methol of attack. Unfortunately Leveuf carried out this procedure in only a few cases. His report was on only three altogether. My first case done in October of that year with a large metastatic hypogastric gland is still free of recurrence. From that time up to October, 1942, my associates and I have done 175 iliac lymphadenectomy operations. Seventy of these were done over five years ago. The low primary mortality and the relatively high survival rate in the five-year cases have convinced me that the addition of iliac lymphadenectomy to the thorough radiation of the primary tumor in Group II cancer of the cervix is of definite value.

*Presented, in modified form, at a meeting of the San Francisco Gynecological Society, March 12, 1941.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their ''Original Communications.''

Selection of Cases

The first problem to be faced was how far one could go in extending the indications for this operation. In the first three years I attempted it in eight Group III cases with extension of the disease to the pelvic wall. Three of these women died postoperatively, and I decided that this demonstrated a definite contraindication. These cases have not been included in the present series. On the other hand, I have also considered the question of Group I cases. In the past five years I have done this operation in five patients with extensive cervical involvement, but in whom the question of parametrial involvement was open to debate. In these cases there was usually some good reason why a Wertheim operation would have meant a considerable added operative risk. I still believe that the Wertheim operation with gland removal is the best procedure in the majority of early Group I cases. For persons untrained in the technique of the radical hysterectomy, I believe it safer and better to do the lymph gland operation with radiation of the cervix rather than an extensive Wertheim procedure. I can say without hesitation that iliac lymphadenectomy is a much easier and safer operation. Naturally certain fundamentals must be learned as in any surgical procedure.

From 1930 to 1935, my service at The Barnard Free Skin and Cancer Hospital, where all but eight of these operations were done, was shared with the late George Gellhorn. Since he in his six months' service used only radiation in the treatment of these Group II cases, and since the radiation technique was the same in my six months' service, this circumstance provided the ideal control for the value of the additional lymphadenectomy operations, as will subsequently be demonstrated. Since 1936, the service has been continuously in my charge, and during this time about 75 per cent of Group II cases have been subjected to the combined lymph gland and radiation treatment. Naturally certain cases were found not suited to operative procedures. Most numerous were those whose adiposity made abdominal intervention an added risk. Advanced years and debility were another contraindication. Diabetes, heart disease, nephritis, and persistent leucopenia were listed among the reasons for advising against surgical intervention. Younger individuals were given preference. Eleven were between 21 and 29 years of age, and the average age of the gland operation cases was several years lower than that of those not subjected to surgery.

Outline of Treatment

In the first three years very little, if any, preliminary deep x-ray therapy was given. The treatment with radium was synchronous with the operation. Taking advantage of the open abdomen, six to eight radon seeds were implanted in the sacrouterine and broad ligament area, totaling about 1,200 mc.hr. From below after closing the abdomen, radium capsules were applied in the usual manner. Two postoperative

deaths occurring in these years were in my opinion attributable to this conjunction of radium treatment with operation. One was due to embolus following radon seed implantation close to the uterine vein; the other was caused by peritonitis following the perforation of a radium capsule into the broad ligament. For this reason, since 1935, the operation has always been made a separate procedure. Previous to this time, radium was given 21 times with operation, 9 times before operation, and 6 times after operation. In the patients operated upon since January, 1936, radium was given 26 times before operation, and 113 times after operation. The absence of uniformity in this program was due partly to difficulties of hospitalization in our overcrowded institution, and partly to the fact that a number of patients had previously received radium treatment elsewhere.

The preferred plan of procedure at present is to have patients begin a course of x-ray therapy four times a week for about four to five weeks through six portals, two anterior, two posterior, and two perineal. The average x-ray dosage has been increased in the past twelve years as follows: Cases 1 to 35, 800 r. skin dose; Cases 36 to 70, 3,730 r. skin dose; Cases 71 to 105, 6,040 r. skin dose; Cases 106 to 140, 8,900 r. skin dose; Cases 141 to 175, 11,000 r. skin dose (2,500 to 3,000 r. tumor dose). The midline area where the operative incision was to be made, was protected and in no case was there necrosis of the operative wound suggesting x-ray damage. At the conclusion of the four to five weeks' x-ray treatment, the patient was again examined to make a final check on the question of lymphadenectomy. An appointment was then made for admission to the hospital two weeks later for operation. Unless there had been serious postoperative wound infection or phlebitis, the radium treatment was given eleven to fourteen days following operation, so that the patient's hospitalization did not exceed two to three weeks. The radium treatment averaged 4,500 mg. hours in the earlier period, but recently has been increased to 5,000 or 6,000 mg.hr. Originally radium was applied from two or three points, often concentrating large dosages in the cervix with increased tendency to necrosis and hemorrhage. In the last six years the application has been from five to six points (corpus, cervix canal, against cervix, vaginal fornices), using a total of 125 to 135 mg. in $\frac{1}{2}$ mm. platinum for forty to forty-five hours. My associate, Dr. A. N. Arneson, has had charge of these applications.

Operative Technique

Spinal anesthesia was employed in almost every case unless contraindicated by high blood pressure. It was frequently supplemented in longer operations by the administration of drop ether in small amounts. The intestinal relaxation produced by spinal anesthesia was helpful in getting the good exposure of the deep pelvic structures necessary in this operation. The first step of the operation consisted in the removal of the tube and ovary. Then a forceps caught the round ligament $1\frac{1}{2}$ inches from the uterus and another clamped the posterior sheath of the broad ligament (Fig. 1). Two fingers separated the peritoneal layers and exposed the structures in the iliac triangle. In all but three cases the ureter lay adherent to the posterior sheath, easily recognized as it crossed the pelvic brim. The external iliac artery and vein could readily be exposed by pressure with a gauze sponge. The internal iliac artery and vein were more deeply situated and visible only at the point of

bifurcation.   Lying as a rule over the origin of the external iliac vessels
but occasionally pocketed in the bifurcation itself was the hypogastric
gland (Fig. 2).   This gland lay in a thin fibrous and fatty network.   By
means of a blunt-pointed forceps or scissors, it could be separated from
the large vessels without trouble.   Two or three small nutrient vessels
were caught and ligated.   Not infrequently there were two such hypo-
gastric glands.
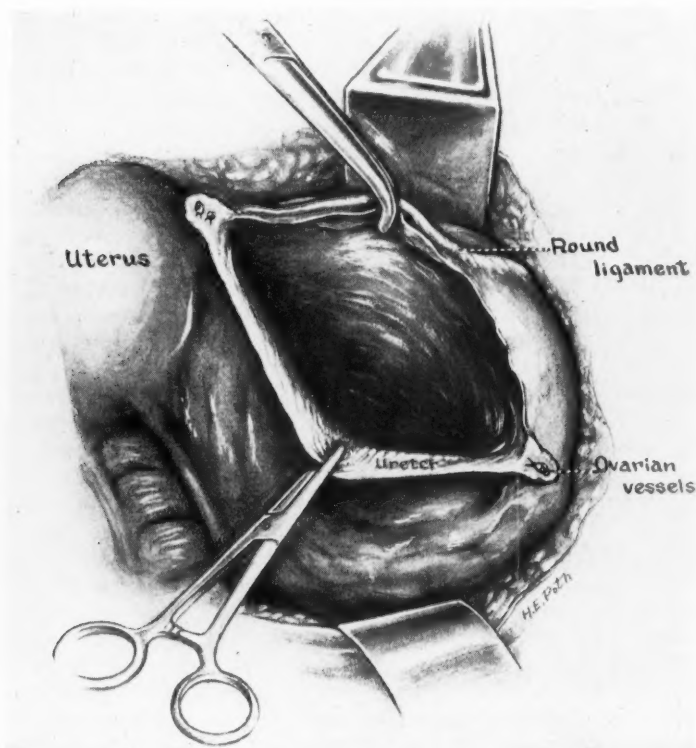
Fig. 1.—Iliac lymphadenectomy.   After removal of the tube and ovary forceps are
applied to the round ligament and posterior peritoneal sheath of the broad ligament
and the tissues of the broad ligament exposed.   The ureter is seen clinging to the
posterior sheath.

The next step was exposure and removal of the obturator glands with
surrounding fat (Fig. 3).   These glands were pocketed beneath the ex-
ternal iliac vein, running parallel to it and clinging to the pelvic wall.
To reach them the tissues of the broad ligament had to be opened more
widely.   This exposed first the obliterated hypogastric artery, rising
from the internal iliac artery.   The obturator gland, or glands, could
usually be felt and by gently pinching between the index and middle
fingers could be freed from surrounding fibrous strands so that the tissue
could be caught by a forceps.   Since the obturator nerve runs directly
through the mass of fat and glandular tissue, the exposed tissues were
grasped lightly and lifted upward, thus exposing the glistening white
band of the obturator nerve beneath.   The obturator chain of glands
was then dissected free and nutrient vessels caught and ligated.   One
long thin obturator gland was almost invariably found running to the

femoral ring. At this stage of the operation, the lateral half of the
broad ligament was completely denuded of lymph glands, fat and fibrous
tissue exposing what I have called the *three white lines:* (1) the
ureter, (2) the obliterated hypogastric artery; (3) the obturator nerve.

Removal of the external iliac glands is relatively easy (Fig. 4). They
lie over the external iliac vessels near the point of exit of these vessels
from the abdomen. Metastases have been so rarely found in these glands
that in cases where there have been technical difficulties in removing
the hypogastric and obturator glands, it has not always been deemed
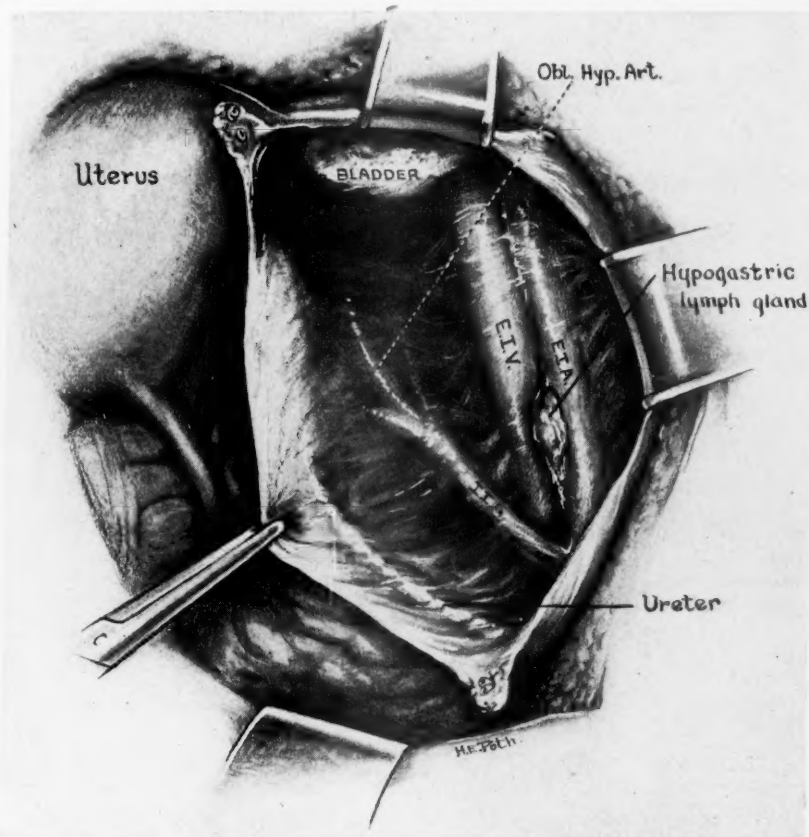
Fig. 2.—Iliac lymphadenectomy. Deeper exposure of the tissues in the lateral
portion of the broad ligament reveals the external iliac artery (E.I.A.) and vein
(E.I.V.) and the internal iliac artery (I.I.A.). Near the bifurcation of the arteries
can be seen loose connective tissue containing one or more *hypogastric* lymph glands.

advisable to prolong the operation by this added procedure. In a limited
group of cases, palpation of the point of crossing of the ureter and the
uterine vessels revealed a small hard ureteral gland. If no such gland
could be palpated, this area was not widely opened up. Where such a
palpable ureteral gland was found, the uterine vessels were doubly
ligated and the gland removed after following the ureter to this point.
Routine ligation of the uterine vessels as suggested by Duncan was done
in three cases, but it was felt that this might predispose to necrosis of
the cervix when radium was subsequently applied, and hence has not
been adopted as a part of the operative technique.

Closure of the operative wound in the broad ligament is effected by suturing the round ligament to the sacrouterine ligament at a point approximately 1½ inches lateral to the uterus (Fig. 5). This suture serves to obliterate the dead space in the broad ligament and prevent the collection of blood and serum in this area. Peritonization of the remaining wound is accomplished by a running stitch. A similar gland removal is then done on the other side and the abdominal incision closed in the usual manner without drainage. The operation takes approximately one and one-fourth to one and one-half hours and is not attended by any
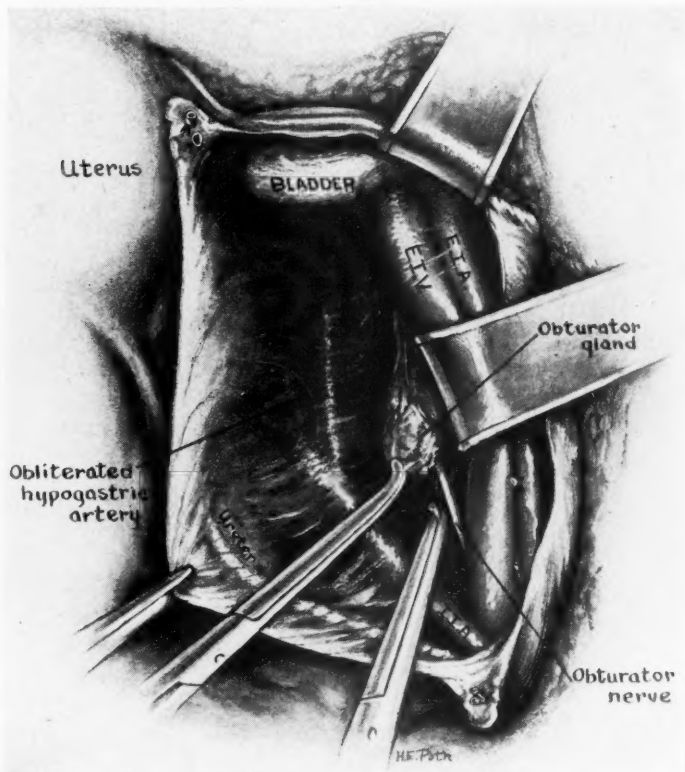
Fig. 3.—Iliac lymphadenectomy. After removing the hypogastric glands, the tissues beneath the external iliac vein close to the pelvic bone are freed and at this point the *obturator* lymph glands are noted. These glands are lifted away from the obturator nerve, clamped off and excised. One elongated gland is usually found running beneath the external iliac vein toward the obturator foramen.

shock unless hemorrhage has occurred. Postoperative morbidity is unusual. It consists of occasional minor wound infections and in four instances a low-grade pelvic or femoral phlebitis. In one case an iritis was associated with and was possibly the result of such a phlebitis. It produced no permanent damage to the eye.

Most gratifying was the low primary operative mortality. In Case 4 and Case 34, the deaths could with great probability be largely attributed to the associated radium treatment. The next operative death, due to infection, did not occur until Case 142, leaving a lapse of 107 cases without a mortality. In the total of 175 patients operated upon up to October, 1942, there were therefore only 3 deaths, a primary operative
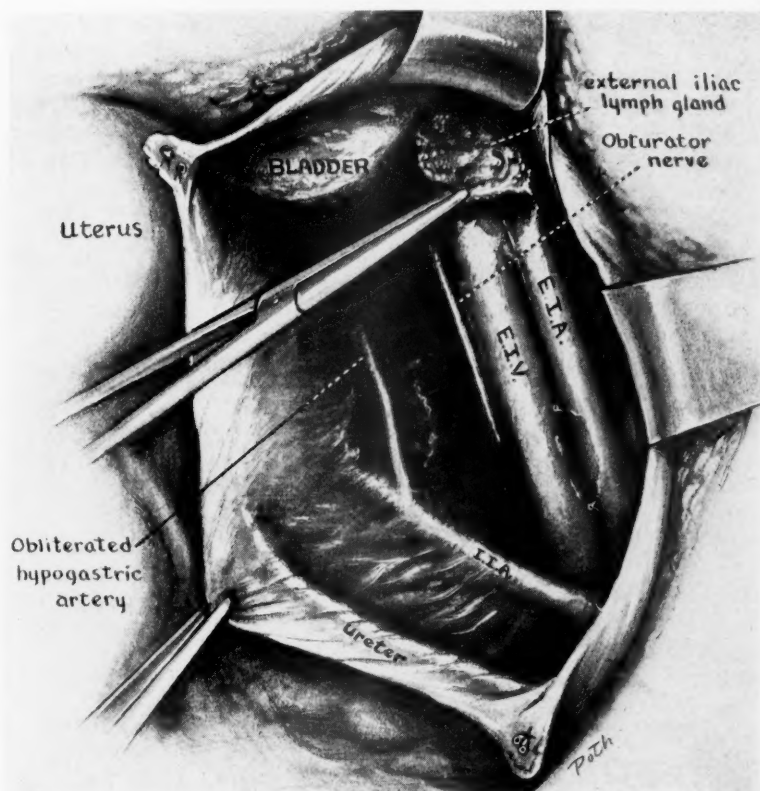
Fig. 4.—Iliac lymphadenectomy. At this point three white bands are seen crossing the base of the open space: (1) the ureter; (2) the obliterated hypogastric artery; (3) the obturator nerve. Now the *external iliac* glands are detached from their site near the inguinal ring and excised.
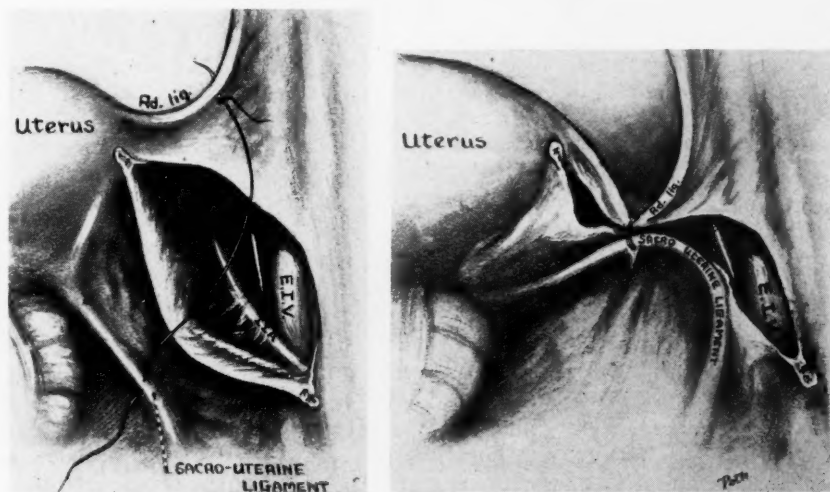
Fig. 5.—Iliac lymphadenectomy. Occasionally a small *ureteral* gland is found near the crossing of ureter and uterine vessels and removed. Closure of the dead space in the broad ligament is accomplished by suturing the round ligament to the sacro-uterine ligament at a distance of about one and one-half inches from the uterus.

mortality of only 1.72 per cent, and in the last 140 cases, a mortality of 0.7 per cent. The dissections in the last seven years have been far more extensive and the number of lymph glands removed almost twice as great as in the first five years, and yet the operative mortality has been less than 1 per cent. Certainly no one can any longer maintain that this procedure is not justified because of its surgical risk.

Technical Difficulties

Since some of these lymph glands are only 1 to 2 mm. in diameter, it is at times no easy matter to locate them. This is particularly true of the important hypogastric glands. At times the most careful palpation after opening the leaves of the broad ligament reveals nothing. The gland may lie not in the iliac triangle but lateral to the external iliac
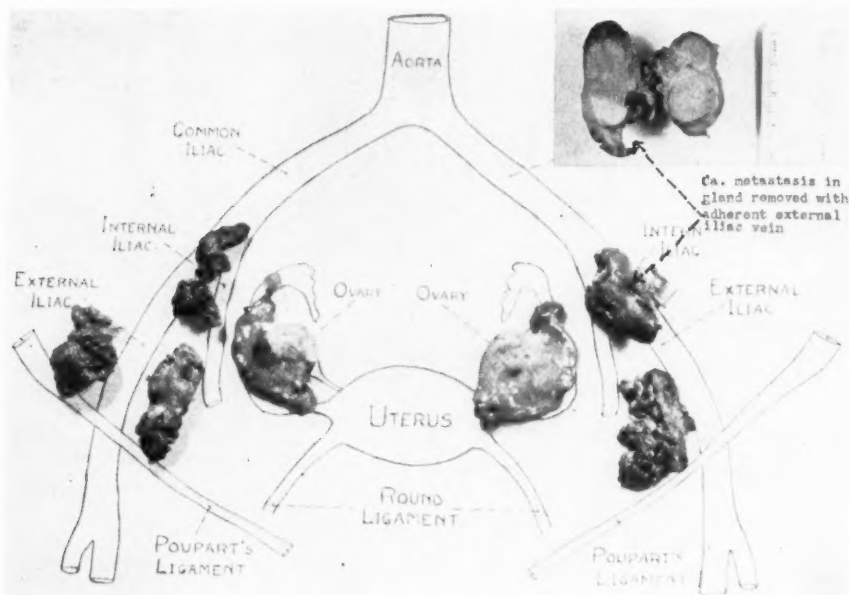
Fig. 6.—Photograph of lymph glands removed by operation, placed on a phantom showing anatomic distribution. In this case the left hypogastric gland was cancerous and densely adherent to the external iliac vein, requiring resection of the vein. Section of this gland and vein seen in the upper right corner.

artery between it and the psoas muscle. Careful dissection of the entire fibrous fatty sheath over the large vessels will usually disclose one or two small glands. In fact the larger glands are more easily removable. Size of the gland is no sure index of metastases. The large ones often show no cancer, while the small ones may contain them. The obturator and external iliac glands are uniformly larger and their anatomic distribution more constant.

A serious operative difficulty is extensive adhesions to the external iliac vessels. Heavy preoperative radiation predisposes to such adhesions, often associated with cancerous invasion of the lymph gland. In three of my earlier cases the extensive firm adhesion of such a gland to the external iliac vein made me desist from its removel, but since I have

found that the external iliac vein and even the external iliac artery can be ligated and a section of the vessel removed with the adherent gland (Fig. 6), I have not hesitated to go ahead with this radical procedure. In none of the six patients in whom this was done was the resultant circulatory disturbance more than temporary. In five cases the vein and in one the artery was resected. Three of these cases which were done between two and one-half and over four years ago showed large metastases in the lymph gland removed in conjunction with the vessel, and all three are still free of recurrence. In one patient, two hypogastric glands were removed with a section of the external iliac vein. The hard gland adherent to the vein, showed no carcinoma, only fibrous strands with a rim of lymphocytic tissue, whereas the nonadherent softer gland lying beneath the reseted vein showed a large cancer metastasis. I am at a loss to explain the findings in this case.

Hemorrhage was not infrequently an operative complication, especially since wider dissections have been practiced. In eleven patients the hemorrhage was disturbing but in no case was it fatal. Almost always the bleeding originated in the plexus of veins at the point where the internal iliac vein divides into its branches. These veins are very friable. In the first cases, I tried to catch these veins with forceps and attempted to pass a needle with ligature around them. Invariably the needle would puncture another vein and the bleeding increased. Three of the earlier cases of severe hemorrhage were left open with clamps and a gauze pack to control the bleeding. Clamps and gauze were removed in forty-eight to seventy-two hours. Recently the cases have been handled far more successfully by a firm gauze pack with a strip of the rectus abdominis muscle applied against the bleeding area to promote coagulation. In fifteen to twenty minutes the bleeding was usually controlled and the operation could be concluded. In two cases a small gauze pack was left in the broad ligament for forty-eight hours. In the remaining 6 cases the bleeding was fully controlled and the pack removed before closure. This excessive bleeding can usually be avoided by more gentle manipulations in the deeper portions of the broad ligament.

Injuries to important viscera or nerves are rare. The bladder is out of the operative field. The ureter must be watched especially if large cancerous glands are present as it may then be adherent to them and stripped off of its normal attachment to the posterior sheath of the peritoneum. Once I ligated the ureter but without harmful result to the patient. Once the obturator nerve was resected with an adherent obturator gland but produced only temporary discomfort.

Associated Conditions

In five patients a supravaginal hysterectomy had been previously done. In these cases of cancer of the cervical stump, the technique of the lymph gland removal was not appreciably complicated. In one patient an operable adenocarminoma of the corpus was found to be associated with the inoperable squamous-celled carcinoma of the cervix and the corpus was removed in conjunction with the lymphadenectomy. I have also recently done an iliac lymphadenectomy (not included in this series) in a case of primary cancer of the upper vagina. This patient with complete local regression following radiation showed cancer in the obturator glands of both sides and died two years later of a recurrence in the right sacral gland.

Most numerous were the cases of adnexal disease. These consisted of chronic salpingitis, hydrosalpinx, cystic ovaries and endometrial cysts of the ovary. Myomas of the uterus were encountered 14 times. In eight women the tumors were so large as to make myomectomy or a supravaginal hysterectomy indicated for technical reasons. In one patient a huge ovarian cyst reaching to the edge of the ribs had to be removed before the lymphadenectomy could be done.

Of special interest were two cases of pregnancy complicating the cervix carcinoma. One patient was three months pregnant and aborted following the radium treatment which in this case preceded the lymphadenectomy. The other was a woman with a Group II cervix cancer who was pregnant about twenty-seven weeks. She was given no preoperative radiation. A cesarean section was done and a living but premature child obtained, which, however, died six hours later. The section was followed by a high Porro hysterectomy and a double-sided lymphadenectomy. X-ray treatment was begun two days after operation, and at its completion four weeks later radium was applied from below. This patient died of a local recurrence eighteen months later.

Glandular Involvement

In every case, each special group of glands was placed in a separate bottle and duly labeled (hypogastric, obturator, external iliac, ureteral, right or left) so that the exact points of metastasis could be distinguished. A total of 1,137 glands were removed, an average of 6.5 glands per case. In order of frequency, cancer was found in the: (1) hypogastric, (2) obturator, (3) ureteral, and (4) external iliac gland. When metastasis was present, more than one gland was often involved. Metastases were sometimes bilateral. Of the 175 cases studied in this way, 47 showed evidence of carcinoma in the removed glymph glands. This incidence of 26.8 per cent is lower than that shown in earlier reports (33 per cent in 1936). Apparently this was due to the prolonged and heavy x-radiation patients have received preoperatively in recent years. The marked disintegration of lymph follicles and the extensive replacement of lymphocytes by fibrinous hyaline and fatty tissue in those glands that were thus heavily radiated bears testimony to the destructive effect of the x-rays. Experience in the treatment of other cancers with deep x-ray therapy would lead one to believe, however, that cancer metastases may frequently be rendered unrecognizable but not wholly destroyed, so that the tumor recurs after a certain time. Moreover it must be borne in mind that unless every gland is examined in serial sections, minute points of metastasis may be overlooked. Such minute metastases have from time to time been noted, even though, for reasons of economy, it has been impractical to make more than a few sections from each gland. The gross appearance of the gland gives no reliable information on the question of metastasis.

Five-Year Results

The crucial test of the value of iliac lymphadenectomy lies in the analysis of the five-year salvage. To compare results in one institution with those in another is most unsatisfactory. Methods of classification into groups and methods of therapy, even though labeled the same, are

likely to be different.   It was therefore fortunate that for a five-year
period through the alternating six months' services of Dr. Gellhorn
and myself at The Barnard Free Skin and Cancer Hospital, a fair basis
for comparison was obtainable.   As shown in Fig. 7, we have the five-
year survival curve of 70 cases of Group II (League of Nations classifi-
cation) cancer of the cervix in which radiation of the cervix was associ-
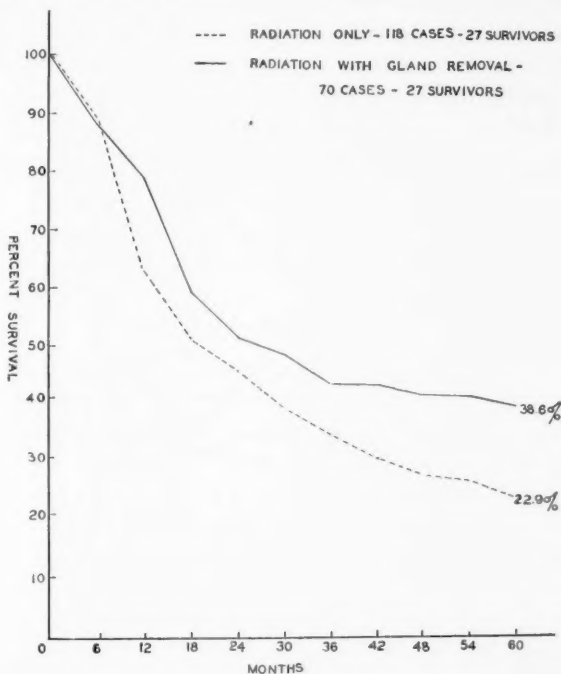
Fig. 7.—Five-year survival curves of two series of cases treated at Barnard Free
Skin and Cancer Hospital, by similar radiation, one *with*, and one *without* iliac lym-
phadenectomy.
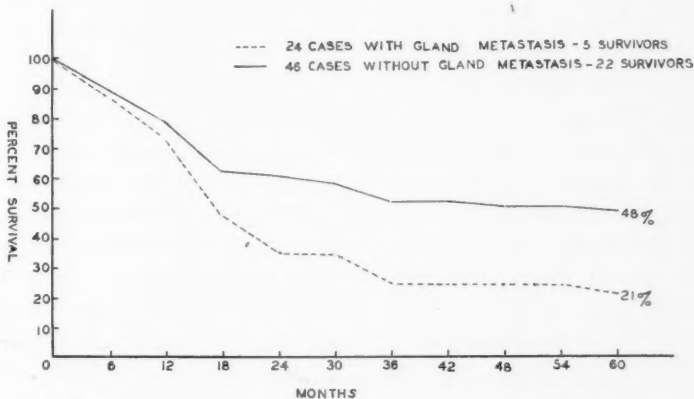
Fig. 8.—Five-year survival curves of 46 iliac lymphadenectomies without cancer
present in removed lymph glands, compared with 24 cases with cancer metastasis.

ated with lymph gland removal and 118 cases of the same group in which radiation alone was used. During this period I subjected a certain number of the Group II cases on my service to radiation only and during Dr. Gellhorn's service all the Group II cases were subjected to radiation without iliac lymphadenectomy. The staff of associates, hospital material, method of classification, and technique of x-ray and radium treatment were identical. Four cases could not be traced after a period of two or more years. In each case they were considered as dead from the time of last information. The percentage of five-year survival was over 15 per cent better in patients who had the additional procedure of iliac lymphadenectomy; or, to put it from the standpoint of patients saved, over *68 per cent additional* were saved by this operation.
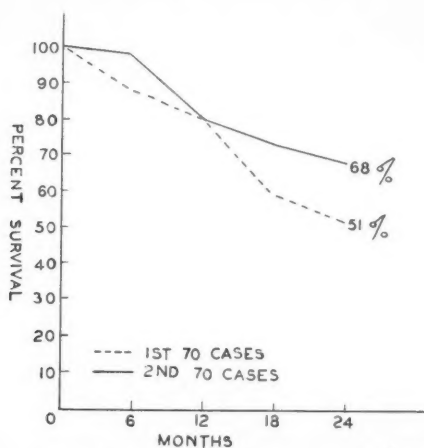
Fig. 9.—Two-year survival curves of the first 70 cases of iliac lymphadenectomy compared with the second 70 cases. Better results in the second series, largely due to improved methods of radiation and more extensive gland removal.

By dividing up the 70 cases treated over five years ago in accordance with whether or not cancer was found in the lymph glands removed, we find an interesting comparison as shown in Fig. 8. As was to be expected, the salvage was definitely less where cancer was found present, the ratio being approximately 2 to 1. On the other hand it is clearly shown that even in the presence of cancer metastasis in the lymph glands, the patient is not necessarily doomed to die. This has been strikingly proved by me in my reports on vulvar cancer. It is also true to a lesser degree of cervix cancer. The case records tabulated in Table I show in brief the history and findings of nine patients having cancer metastasis in the lymph glands that survived longer than four years. Of particular interest are Case 1, now over twelve years free of recurrence, and Cases 7 and 9, in which a metastatic gland adherent to the external iliac vessels required resection of the vessel in order to remove the gland.

Since there was considerable improvement in the radiation technique employed since 1937, we are anticipating better final results in the group of cases operated since that time. An indication of this is given in Fig. 9 in which we compare the two-year salvage of the first 70 cases with the second 70 cases in my series. The result of better technique is apparent in the second year.

Arguments Against Iliac Lymphadenectomy

1. It may be claimed that this operation is a highly technical procedure, attended by a considerable mortality and complications. The experience in these 175 operations has demonstrated it as a relatively safe and simple procedure, once certain points in anatomy and technique are learned. A short period of training should enable the average surgeon to acquire the necessary skill.

2. A further objection that has been raised is that the operation does not constitute a block dissection as practiced in breast and oral cancer. In a sense it must be acknowledged that this is true. On the other hand, anatomical conditions in the pelvis differ greatly from those in the axilla and neck. In the latter the lymph glands lie in a more or less continuous mass of fat and connnective tissue that can be removed en masse. In the pelvis the important tributary lymph glands lie in a more veil-like sheath of loose connective tissue, pocketed between and beneath the large vessels. While it is not feasible on this account to remove them in continuity, we can clean out the lateral half of the broad ligament area on each side as thoroughly as in an axillary dissection. Just as the latter does not ordinarily include the supraclavicular chain, so the iliac lymph gland operation does not include the sacral glands. My procedure is at least 80 per cent complete and hence I believe is amply justified. Extrapelvic gland metastasis, as has long been demonstrated, is not the rule, even in cases coming to autopsy.

3. Finally, the operation has been opposed by radiologists, who claim that with recent improvements in deep roentgen therapy, cancer in the pelvic lymph glands can be destroyed by radiation as completely as removed by surgery. I do not deny the value of such prolonged radiation and the microscopic studies made in removed lymph glands in my cases show that after heavy radiation, cancer is less frequently noted. Nevertheless we have no evidence that this apparent disappearance of metastases is permanent. It does not compare in therapeutic certainty with the surgical excision of these glands. It has long been demonstrated that the removal of axillary lymph glands in breast cancer even when found free of metastases is justified by clinical experience. In similar manner I feel that even though cancer may be found in the pelvic lymph nodes in not more than one out of every four or five cases after heavy x-radiation, the surgical excision of such nodes is justified.

TABLE I. CASES OF CERVIX CANCER WITH LYMPH GLAND METASTASIS SURVIVING LONGER THAN FOUR YEARS

CASE RECORD AGE	SYMPTOMS	INVOLVEMENT	X-RAY TREATMENT	RADIUM TREATMENT	OPERATIVE NOTES	GLANDS	SUBSEQUENT COURSE
(1) S. S. No. 45286 (51 yr.)	Vaginal bleeding 6 months	Cauliflower lesion. Both parametria involved	None	Oct. 14, 1930 4,900 mg. hr. Dec. 23, 1930 800 mg. hr. Total 5,700 mg. hr.	Oct. 14, 1930 Two palpable hypogastric glands removed 8 radon seeds introduced abdominally in para-metria	Left hypogastric gland, size of wal-nut, full of cancer	Complete local regression Clinically well, Nov. 6, 1942 (12 yr.)
(2) L. S. No. 45691 (42 yr.)	Bleeding 4 months	Both parametria infiltrated	None	Dec. 2, 1930 2,850 mg. hr. Dec. 30, 1930 1,725 mg. hr. 1931-1933 3,600 mg. hr. Total 8,175 mg. hr.	Dec. 2, 1930 Typical operation with radon seed abdominal implantation	Four glands removed Large metastasis in left hypogastric	Repeated small local recurrences Jan. 23, 1935, left inguinal gland containing cancer removed Died Oct. 5, 1935, recurrent (4 yr., 10 mo.)
(3) I. F. No. 48693 (40 yr.)	Bleeding for several months	Parametria and vaginal fornix involved	Feb. 2, 1932 1,800 r. units Sept. 13, 1932 700 r. units	Nov. 10, 1931 3,350 mg. hr. Dec. 22, 1931 1,200 mg. hr. Total 4,550 mg. hr.	Nov. 10, 1931 Typical operation with radon seed abdominal implantation	Four glands removed Two hypogastric glands metastatic	Clinically well but ureterovaginal fistula developed Dec. 8, 1932 Recurrence developed in 1939. Died Aug. 1, 1939 (7 yr., 9 mo.)
(4) A. C. No. 48954 (31 yr.)	Discharge 2 months	Slight parametrial involvement	None	Dec. 15, 1931 3,400 mg. hr. Jan. 26, 1932 1,200 mg. hr. Total 4,600 mg. hr.	Dec. 15, 1931 Typical operation with radon seed abdominal implantation	Seven glands removed Left hypogastric showed cancer	Uneventful course Clinically well June 16, 1942 (10 yr., 6 mo.)

(5) H. S. No. 66682 (59 yr.)	Bloody discharge at intervals for 2 years	Right parametria thickened	Nov. 19, 1936 3,200 r. units Feb. 13, 1941 to April 8, 1941 8,000 r. units	Jan. 2, 1937 4,000 mg. hr. Oct. 18, 1941 1,400 mg. hr. Total 5,400 mg. hr.	April 24, 1937 Difficult operation, ligated external iliac vein	Nine glands removed Cancer metastasis in left and right hypogastric	Small local recurrence Oct. 1, 1941 Clinically well July 3, 1942 (5 yr., 3 mo.)
(6) G. S. No. 69060 (54 yr.)	Bleeding every 2 weeks for 1 year	Both parametria thickened	July 23, 1937 5,600 r. units	Aug. 11, 1937 5,000 mg. hr. Jan. 26, 1938 680 mg. hr. Total 5,680 mg. hr.	Oct. 8, 1937 Operation difficult Gland adherent to right external iliac vein	Six glands removed Large metastasis in right hypogastric gland	Clinically well Aug. 30, 1942 (5 yr.)
(7) A. W. No. 70305 (51 yr.)	Bleeding for 4 months	Left parametria thickened Myomatous uterus	Nov. 9, 1937 5,600 r. units	Dec. 29, 1937 2,500 mg. hr. Jan. 5, 1938 2,500 mg. hr. Total 5,000 mg. hr.	Dec. 11, 1937 Operation including supracervical hysterectomy for myomata Resection of left external iliac artery with adherent lymph gland	Five glands removed Large necrotic metastasis in left hypogastric	No sequelae from ligation of artery Clinically well July 6, 1942 (4 yr., 7 mo.)
(8) G. B. No. 70678 (39 yr.)	Prolonged menses 2 years	Both parametria involved	Dec. 17, 1937 5,600 r. units	Jan. 29, 1938 3,500 mg. hr.	Jan. 5, 1938 Typical operation	Ten glands removed Left obturator showed cancer	Clinically well Oct. 28, 1942 (4 yr., 10 mo.)
(9) E. W. No. 71896 (46 yr.)	Bloody discharge 1 year	Left parametria thickened	May 5, 1938 5,000 r. units	Feb, 1938 7,500 mg. hr. (?) given elsewhere	April 23, 1938 Difficult operation Left external iliac vein resected with adherent gland	Nine glands removed Large metastasis in left hypogastric gland	Clinically well June 30, 1942 (4 yr., 2 mo.) (See Fig. 6.)

Summary

1. One hundred and seventy-five cases of Group II cervix cancer were subjected to iliac gland removal with radiation of the primary tumor. The operative mortality in this group was 1.7 per cent with a mortality of 0.7 per cent in the last 140 cases.

2. The five-year survival rate of 70 cases operated previous to October, 1937, was 38.6 per cent. Comparing this with a five-year survival of 22.9 per cent in 118 similar cases treated by radiation alone, there was a 68 per cent greater salvage when the lymph gland removal was added to the radiation treatment.

3. Cancer was found present in the lymph glands in 26.8 per cent of the 175 cases operated upon. Even in those cases with demonstrated metastases, a five-year salvage of 21 per cent was obtained.

4. This experience extending over a period of twelve years has, I believe, firmly established iliac lymphadenectomy as a valuable adjunct in the treatment of Group II cancer of the cervix.

AN ANALYSIS OF SOME FACTORS ASSOCIATED WITH THE DEVELOPMENT OF PRE-ECLAMPSIA

With Special Reference to Extracellular Water Measurements in 1,388 Patients

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M ANY publications indicate that rapid or excessive weight gain often points to water retention which may be a harbinger of pre-eclampsia. It has been recognized that many patients having abnormal weight gains have not accumulated excessive water, but rather have laid down protoplasm or fat (Waters[1]).

In a previous paper,[2] we have reported measurements of the thiocyanate-available water (roughly equivalent to the extracellular water) in 180 cases of human pregnancy. Patients who had excessive available water, but who were clinically normal, showed a 23.1 per cent incidence of pre-eclampsia developing subsequent to the test. In contrast, patients with normal water had a toxemia incidence of only 1.42 per cent.

Since we were interested in selecting potential toxemia patients for special study, we have routinely determined the available water in almost all of our clinic patients (who were registered early enough) from October, 1941, through June, 1942. In all, and including the published series, 1,388 patients were given the test at least once; 552 of these had

2 or more tests. All measurements were made after the thirtieth week of gestation, usually at about thirty-two to thirty-six weeks.

In the present study, we shall analyze this series for a number of factors which might conceivably affect the incidence of excessive water and of toxemia. An evaluation of the test will be attempted.

In the following discussion, the terms "available water," "extracellular water" and "water" will be used more or less interchangeably. This, of course, is inexact but will save circumlocution.

Methods

Each patient was given 1,000 mg. of sodium thiocyanate in fruit juice, by mouth. (In the first 180 cases, previously reported, the thiocyanate was given intravenously.) The patient was asked to save all of her urine and come back the following morning, at which time the urine collection was completed, and a blood sample was drawn with minimal or no stasis. The period thus allowed for the distribution of thiocyanate in the extracellular water varied from eighteen to twenty-four hours, and was usually close to twenty-one hours.

Thiocyanate in serum and urine was determined in duplicate with the Evelyn photoelectric colorimeter, by a method described elsewhere.[3] The completeness of urine collection was checked by measurement of the creatinine excretion, using the method of Folin.[4] The test was discarded if considerable volumes of urine obviously had been lost.

The "available water" was calculated in terms of percentage of body weight, since we felt that the usual formula for surface area might not be valid in late pregnancy.

Serum proteins were determined in duplicate, one sample by the method of Wong[4] and one by that of Howe and Koch and McMeekin.[5] Recorded results checked within 2 per cent.

Relation of Excessive Water to Toxemia

In the tables to follow, the number of patients will not always agree because the specific information for many patients was not available, or the patients had not been observed over long enough a time in pregnancy. Two-thirds of all patients with excessive extracellular water were placed on low salt diets as soon as the abnormality was found. This may have affected the incidence of toxemia.

Fig. 1 shows the distribution of normal and abnormal values for the available water. The incidence of excessive water in the 1,388 patients was 19.96 per cent, in good agreement with the 21.66 per cent found in the first series of 180 patients.

The incidence of pre-eclampsia in the whole series was 7.71 per cent. In patients with excessive water, the incidence of subsequently developing pre-eclampsia was 22.75 per cent (compare 23.1 per cent in the original series), while in patients with normal water *at the time of the test*, the toxemia incidence was 3.96 per cent. This last figure is somewhat higher than the 1.42 per cent originally found, but will be explained below. From these data, it appears that the patient with excessive water was, on the average, about 6 times as likely to develop pre-eclampsia as was the patient with normal water. More frequent measurements of the available water would magnify this difference.

Of the 107 cases of pre-eclampsia, 44, or 41.1 per cent, were in the group of patients showing normal water. Thus the test often failed to select patients who subsequently developed pre-eclampsia. An analysis of such failures reveals several causes which operated separately or together.

Causes for Failure of Test.—1. When the measurement of available water was begun as a routine procedure on our clinic patients, the determination was made at the thirty-fourth week of pregnancy. It was
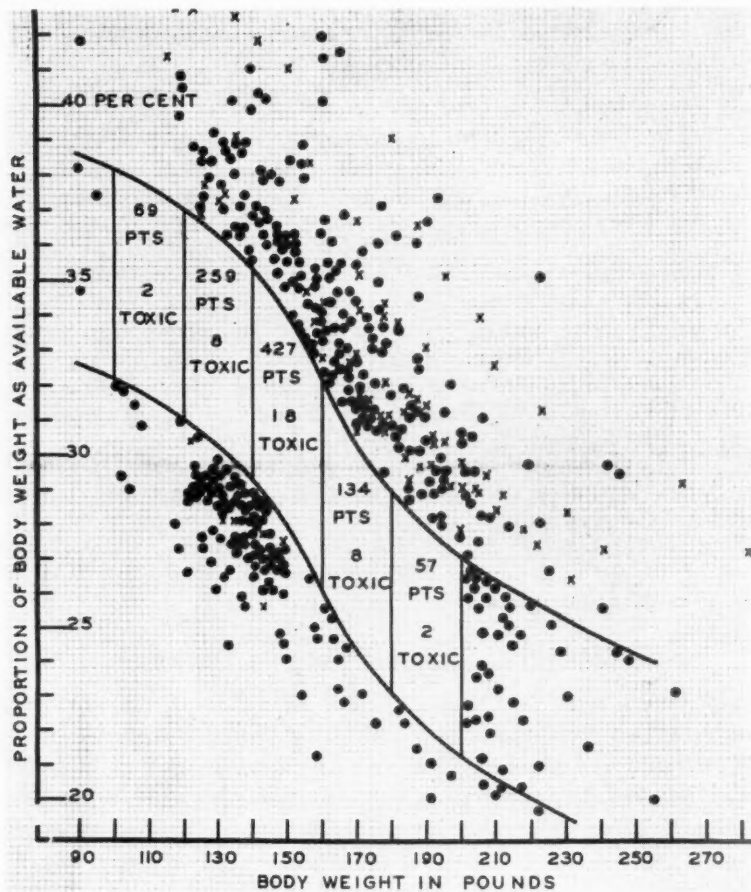
Fig. 1.—The distribution of normal and abnormal values for extracellular water in 1,388 pregnancies. The curves were drawn by the same criteria as previously described.[2]

● = Normal pregnancy
× = Toxemia

soon found that this was frequently too early, since many patients began to accumulate abnormal amounts of available water after this time. As a result of this finding, the routine was changed so that the first measurement of available water was made at the thirtieth to thirty-third week, with the test being repeated at the thirty-fifth to thirty-seventh week. Many (42) patients had normal proportions of water in the first test, and excessive water when repeated; a number of these subsequently

developed pre-eclampsia. Thus water retention often did antedate hypertension, but this observation could be missed by measuring the available water too early. It is this factor which accounts for the higher incidence of toxemia in the "normal water" group in the present paper, as compared with the original series in which nearly all tests were done in the last three to four weeks of pregnancy.

2. We shall demonstrate in a separate study that the restriction of salt in the diet will markedly reduce the volume of available water. Such reduction in available water to normal levels does not uniformly prevent the appearance of hypertension and the rest of the pre-eclamptic syndrome. This fact may often account for the finding of normal extracellular water not only in the "pretoxic" patient, but also in certain patients with manifest toxemia.

Of the 44 patients developing toxemia after a test had shown normal water, 6 had been on a diet, the nature of which was not specified in the chart. Of the 38 remaining, 25, or 65.8 per cent, had been placed on a 2 Gm. salt diet prior to the test. It seems quite possible that the available water in these cases may have been reduced, and that the test was done too late to show any abnormality which may have existed.

3. Cases of eclampsia, and of nonconvulsive toxemia, without clinical edema are not uncommon. Whether such cases occur without any abnormal water retention is unknown, since the body may gain water up to 10 per cent of its weight without visible edema. While a few of our patients with toxemia have had normal values for available water (i.e., not even occult edema was present), dehydration treatment had been used prior to the test. If toxemia does occur without even occult edema, and on the average dietary salt intake, then measurement of available water could not be of prognostic value in such cases.

4. Some patients classified as having pre-eclampsia may rather have labile blood pressures. Possibly these are latent hypertensives who have a simple increase in blood pressure as they approach term. Measurement of occult edema would not be of value in predicting such "toxemias."

5. The possibility of intracellular water retention must not be ignored. Intracellular water is inaccessible to measurement by the thiocyanate method.

Factors Possibly Affecting the Incidence of Increased Extracellular Water and of Toxemia

1. *Serum Proteins.*—It is well known that the plasma proteins play a leading role in maintaining the fluid balance between the blood and the extracellular space of the body. The filtration of fluid out through the capillary walls is impelled by the intravascular hydrostatic pressure. This filtration, normally, is nicely balanced by capillary reabsorption attributable to the oncotic pressure of the proteins. Depletion of the proteins results in decreased reabsorption of the filtrate and edema may occur, as in nephrosis or nutritional edema. Goudsmit and Louis,[6] in a quantitative study, found that a decrease of 1 Gm. of protein per 100 ml. of serum resulted in an increase in extracellular water amounting to 3.8 ± 0.8 per cent of the body weight. Strauss[7] has attributed toxemia of pregnancy (as distinguished from vascular disease) to water retention caused by lowered plasma proteins or excessive sodium intake, or both.

TABLE I. THE RELATION OF SERUM PROTEINS TO WATER RETENTION AND TOXEMIA

DEGREE OF ABNORMALITY IN AVAILABLE WATER	NORMAL WATER		DEGREE OF AVAILABLE WATER INCREASE								TOTALS
			+		++		+++		+++		
Cases	86		94		46		21		19		266
Average serum protein grams per 100 ml.	6.13		6.22		5.92		6.04		6.07		6.12
Percentage of cases with protein <5.50	10.47		9.57		21.74		14.28		0.0		11.65
Percentage of cases with protein <5.75	29.07		20.22		34.78		28.56		31.60		27.05
Incidence of toxemia, per cent	9.31		17.02		21.76		14.28		47.36		17.30
Serum protein level, grams per 100 ml.	LESS THAN 5.75	MORE THAN 5.76	<5.75	>5.76	<5.75	>5.76	<5.75	>5.76	<5.75	>5.76	
Cases	25	61	19	75	16	30	6	15	6	13	266
Incidence of toxemia, per cent	8.00	9.84	21.05	16.00	18.75	23.33	33.33	6.67	66.7	38.5	17.30

We have determined the serum proteins in 86 patients with normal available water, and in 180 with excessive water. The results (Table I) indicate no significant difference between the normals and patients with varying degrees of water retention, either in average levels, or in the distribution of low values. The average serum protein checks well with many published data for normal pregnant women.

A correlation between the serum proteins and the incidence of toxemia does seem to exist, if the available water is markedly abnormal. As Table I indicates, toxemia is more frequent in patients with 3- and 4-plus abnormally high water who also have serum proteins of less than 5.75 Gm. per 100 ml.

2. *Hemoglobin.*—Peters and Eisenman[8] have demonstrated that low hemoglobin levels may often be associated with edema, even in the presence of high normal serum proteins. We found that the average hemoglobin was the same in patients with or without excessive water, and with or without toxemia of pregnancy. However in the patients with excessive water, 26.7 per cent had hemoglobins of less than 80 per cent while in the normal group, 15.7 per cent had hemoglobins below 80 per cent. (Hemoglobin was determined by the Sahli method, and 14.5 Gm. per 100 ml. was considered as 100 per cent.)

3. *Rh Factor.*—The Rh factor, which seems to be a causative agent in erythroblastosis foetalis, has been suggested as perhaps related to toxemia of pregnancy. A possible relation to edema is seen in the fetal hydrops often found in erythroblastosis. The Rh factor was determined in 238 of our cases, and no correlation with excessive water is evident. In 203 Rh positive cases, the incidence of excessive water was 22.16 per cent; in 35 Rh negative cases, 6, or 17.14 per cent, showed increased water. The incidence of toxemia in the Rh positive group was 9.86 per cent and in the Rh negative was 8.57 per cent, not a significant difference. The incidence of Rh negative women was 14.7 per cent, in good agreement with the 14.0 per cent reported by Levine, Vogel, Katzin and Burnham[9] in 1,035 cases.

4. *Parity and History of Toxemia.*—The incidence of excessive water was greater in the multiparas (25.3 per cent) than in primiparas (16.3 per cent). Further analysis shows that this difference is accounted for by those women having a history of previous toxemia, of whom 51.5 per cent had an increased amount of water and 21 to 32 per cent a recurrent toxemia.

Perhaps the disturbance resulting in toxemia in an earlier pregnancy is still operative in some degree in about half the cases, as shown by the water retention.

TABLE II. THE RELATION BETWEEN BODY WEIGHT AND THE INCIDENCES OF EXCESSIVE WATER AND TOXEMIA

BODY WEIGHT	LESS THAN 120 POUNDS		121-160 POUNDS		161-200 POUNDS		MORE THAN 201 POUNDS	
Cases	86		889		343		70	
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
Incidence of excessive water	7	8.14	100	11.25	137	39.95	33	47.15
Incidence of toxemia — All cases	4	4.65	48	5.41	44	12.83	11	15.73
Incidence of toxemia — Cases with normal water	2	2.53	32	4.06	10	4.86	0	0.00
Incidence of toxemia — Cases with excessive water	2	28.58	16	16.00	34	24.81	11	33.33

5. *Weight.*—Matthews and Der Brucke[10] have demonstrated that toxemia of pregnancy shows an increased frequency in women weighing more than 200 pounds. We have divided our patients into weight groups, and found that as the weight increased there is a progressive rise in incidence both of abnormally high water and of toxemia. The increasing incidence of toxemia occurs in those patients with abnormal water, not in those with normal water (Table II).

6. *Weight Gain.*—Since weight gain has been considered important in that rapid or excessive gain may be a premonitory sign of toxemia, we have analyzed our data in several ways, looking for a correlation between amount or rate of weight gain and the incidence of excessive water and toxemia.
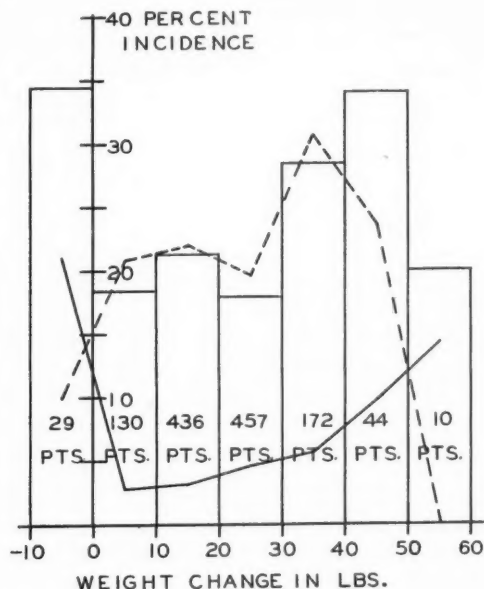
Fig. 2.—The relation between total weight change in pregnancy, and the incidences of excessive available water and toxemia. The columns ☐ give the incidence of excessive water, and the numbers in each column refer to the number of patients in group. The solid line gives the incidence of toxemia in patients with normal available water at the time of the test. The broken line gives the incidence of toxemia in patients with excessive available water.

A. The total weight gain to the time of the last measurement of available water showed no correlation with the amount of water until the gain exceeded 30 pounds. Even then, the incidence of excess water was no greater than in patients who had lost rather than gained weight. However, nearly all patients losing weight did so in consequence of an obesity diet. As demonstrated above, obese patients have a greater incidence of abnormal water.

The incidence of toxemia increased slightly as the weight gain rose (Fig. 2).

B. Rapid gain in weight at any time in pregnancy, prior to the last test, seemed to bear no relation to the incidence of excessive available water. In 709 patients gaining less than 6 pounds per month, the incidence of excessive water was 23.58 per cent; in 483 patients gaining more than 6 pounds, it was 18.02 per cent. The incidences of toxemia were 8.32 and 7.66 per cent, respectively.

C. The weight gain per week, within a month before the test, did not bear any relation to the incidence of excessive available water until the weight gain exceeded 4 pounds per week. Such large gains, which occurred in only 2.6 per cent of all patients, doubled the incidence of excessive water. The incidence of toxemia did increase somewhat as the rate of weight gain became greater. The effect was not well marked until the gain reached 4 pounds per week, and appeared only in those patients with *normal* available water. If these rapid gains represent water retention, the water may be held intracellularly.

D. The weight gain per week after the test tended to be greater in those patients who had increased available water. The abnormal tendency shown by the water retention seemed to predispose to further gain. Ignoring patients who lost weight, in the normal water group, 829 patients gained an average of 1.71 pounds per week after the test, while 198 patients with excessive water averaged 2.21 pounds per week.

The incidence of toxemia increased with the rate of weight gain following the test. This correlation was found only in patients whose available water had been normal when measured (Table III). These patients who gained weight rapidly and went on to develop pre-eclampsia presumably gained water excessively after the test.

TABLE III. THE RELATION BETWEEN RATE OF WEIGHT GAIN AFTER THE TEST AND THE INCIDENCE OF TOXEMIA

WEIGHT CHANGE PER WEEK, AFTER TEST		LOSS IN WEIGHT	GAIN IN WEIGHT, POUNDS PER WEEK								MORE THAN 4½
			0-1	1-1½	1½-2	2-2½	2½-3	3-3½	3½-4	4-4½	
Cases		137	256	174	179	139	124	44	45	27	39
Incidence of toxemia	In all cases; per cent	12.41	6.62	6.90	5.59	7.20	7.27	13.63	13.34	7.41	12.82
	Cases with normal water	8.14	3.30	2.76	1.97	1.93	5.88	8.83	9.09	5.56	8.00
	Cases with excessive water	19.60	23.00	27.60	25.95	22.86	13.64	30.00	25.00	12.50	25.00

7. *Variability in Blood Pressure.*—Browne[11] has described a "warning rise" in blood pressure occurring during pregnancy, which may be observed on a single occasion. He believes that patients showing such upward spikes in pressure are likely to develop toxemia as they approach term. Accordingly, we have analyzed our data in several ways, seeking a relationship between variability of blood pressure and the incidence of excessive water and of toxemia. The rise in blood pressure was broken down into groups of 5 mm. increments, and was calculated as (a) the difference between the highest and lowest pressures, (b) the difference between the highest and the usual (or average, if variable) pressure, and (c) the difference between the pressure at the time of the test and the usual (or average) pressure. All analyses were based on blood pressures observed before the last measurement of available water, and include both systolic and diastolic readings. Since the results of all analyses are about the same, only one set of data will be presented, those of the maximal variation in systolic pressure. In general it may be said that the usual level of blood pressure (see below) is more important than the variability in predisposing to toxemia.

The incidence of excessive water is not influenced by the variability of the blood pressure. The incidence of toxemia shows no significant change so long as the maximal variability in systolic blood pressure is less than 20 mm. Hg; with greater lability of blood pressure, the toxemia incidence nearly doubles, both with normal and with excessive water (Table IV). Thus "warning rises" in systolic pressure, if greater than 20 mm. Hg do have some significance.

TABLE IV. THE RELATION BETWEEN THE MAXIMAL VARIATION IN SYSTOLIC BLOOD PRESSURE AND THE INCIDENCES OF EXCESSIVE WATER AND TOXEMIA

SYSTOLIC VARIATION MM. HG		LESS THAN 10	11-15	16-20	21-25	MORE THAN 26
Cases		339	239	278	179	193
Incidence of excessive water, per cent		21.83	21.36	18.72	25.12	23.82
Incidence of toxemia	All cases, per cent	4.13	7.11	6.48	11.18	16.59
	Cases with normal water, per cent	1.13	4.79	3.54	4.48	8.85
	Cases with excessive water, per cent	14.88	15.68	19.23	31.10	30.44

8. *Usual Level of Blood Pressure.*—The incidence both of excessive water and of toxemia increases with rise in the usual level of blood pressure. In the present series, no patient developed toxemia if the blood pressure had been consistently less than 105/60 mm. Hg preceding the measurement of available water. (Analysis of large groups of toxemias will, of course, show considerable numbers of patients with low blood pressures prior to the onset of toxemia.) Of all patients with normal pregnancies, 73.4 per cent never showed a blood pressure as high as 130 mm. Hg in the systolic, or 80 mm. Hg in the diastolic. In contrast, 72.5 per cent of those developing pre-eclampsia subsequent to the measurement of available water *did* show pressures exceeding 130/80 on at least one occasion, and their blood pressures were usually above 120/70. From the data in Table V and especially from Fig. 3, it appears that the incidence of toxemia increases with 2 factors, either of which is effective alone, and that when these factors are both present, a very high incidence of toxemia may be expected. The factors are increasingly high level of usual blood pressure and the presence of excessive water. Of these 2, the blood pressure level may be more fundamentally important since, excluding chronic hypertension, the incidence of excessive water (accumulated late in pregnancy) seems to increase with each increment in

TABLE V. THE RELATION OF THE USUAL LEVEL OF SYSTOLIC BLOOD PRESSURE TO THE INCIDENCES OF EXCESSIVE WATER AND TOXEMIA

USUAL SYSTOLIC PRESSURE, MM. HG		90-99	100-109	110-119	120-129	MORE THAN 130
Cases		50	267	454	376	125
Incidence of excessive water, per cent		4.00	16.86	19.62	26.06	28.80
Incidence of toxemia	In all cases, per cent	0.00	2.25	4.41	14.10	17.60
	Cases with normal water, per cent	0.00	0.90	2.46	8.28	9.00
	Cases with excessive water, per cent	0.00	8.89	12.37	30.62	38.90

blood pressure. We cannot say whether the higher arterial pressure carries through the arterioles to the capillaries, and thus increases filtration, which in turn leads to an accumulation of edema water. This is probably not the case in most forms of hypertension, since the peripheral resistance is thought to be localized in the arterioles. In consonance with this belief, we found excessive water in only 3 of the 18 patients who were known cases of chronic hypertension. However, in preeclampsia the venous pressure has been reported as lying at the uppermost limits of normal,[12] which suggests that the capillary pressure may be slightly increased.
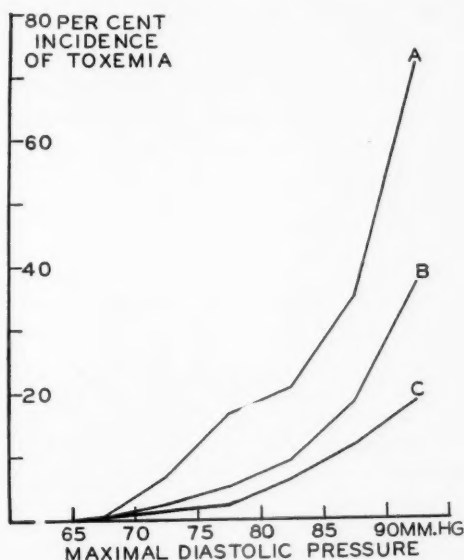
Fig. 3.—The relation between the maximal diastolic pressure as observed at any time during pregnancy, and the incidence of preeclampsia. *A*, patients with excessive available water. *B*, all patients. *C*, patients with normal available water at the time of the test.

9. *Maximal Blood Pressure.*—The maximal blood pressure observed prior to the measurement of available water was found to have a marked effect upon the incidence of toxemia, and a somewhat lesser effect upon the incidence of excessive water. Fig. 3 shows that the incidence of toxemia increases very rapidly as higher maximal diastolic readings are observed. All cases used for their graph were considered as not having toxemia at the time of the test. Those whose maximal diastolic pressure reached 90 or more had shown single upward spikes in the blood pressure, often early in pregnancy.

10. *Time Elapsed From Test to Delivery.*—As might be expected, the longer before delivery one measures the available water the lower is the incidence of abnormal findings, and the higher is the incidence of toxemia in patients whose available water was normal at the time of the test. This merely means that the water retention (at least extracellularly) most frequently begins after the thirty-fourth week of gestation.

11. *Degree of Abnormality of Test.*—The toxemia incidence increases as the measurement of available water shows a greater abnormality. This may be seen by reference to Table I.

Miscellaneous Observations

1. *Time From Test to the Appearance of Hypertension.*—The average period from the demonstration of excessive water to the appearance of hypertension was about four weeks. In those patients having excessive water and subsequently developing pre-eclampsia, 60 per cent showed the first abnormal blood pressure readings in two and one-half to five and one-half weeks after the test. In a few cases (4 per cent) as long as ten weeks elapsed between the finding of excessive water and the appearance of hypertension. In some other cases hypertension may have appeared before the water retention, although this is not certain as pointed out above. A few patients, under dehydration treatment, did have pre-eclampsia without excessive water being found either before or after the blood pressure rose.

In patients developing pre-eclampsia after the test had shown a normal available water level, the average period between the test and the first elevation in blood pressure was nearly six weeks. Thus there was time for many of these patients to accumulate water before developing hypertension. Repeated tests often demonstrated that this had happened (see above).

2. *Relation of Weight Gain to Water Gain.*—In 552 cases, 2 or more measurements of available water were made in the last ten weeks of pregnancy. Comparison of the change in available water with the change in body weight reveals that in 42 per cent of all cases the gain in water exceeds the gain in weight, and in 8.6 per cent there is a gain in water with a loss in body weight.

The simplest of several possible explanations would be that late in pregnancy intracellular water shifts into the extracellular compartment. Dieckmann[13] has suggested such a shift in water to account for the sudden appearance of edema in certain toxemia patients, and McPhail[14] believes that one of the central features of toxemia is cell dehydration arising out of an extensive shift of intracellular water into the interstitial spaces. In many respects toxemia of pregnancy is characterized by exaggerated changes, which in lesser degree are normally incident to pregnancy. Perhaps movement of water out of the cells is a normal occurrence in late pregnancy, and in the toxic disturbances the shift is unusually great.

This hypothetical shift in water (if such it be) is more marked in patients who have an abnormally high available water level, and is still more marked in patients who are normal in the first test and abnormal in the second.

Conversely, in patients who lose weight and water under salt restriction, the loss in available water is almost always greater than the weight loss. This suggests that some extracellular water may shift back into the cells, probably because extracellular sodium is depleted. These data will be presented in more detail in another paper.

The incidence of excessive water increases when the disproportion between water gain and weight gain increases. The incidence of toxemia does not show so regular a correlation.

The average increment in available water, toward the end of pregnancy, is about 250 to 300 ml. per week in patients whose dietary salt intake is unrestricted. Apparently this gain tends to be maintained regardless of changes in body weight. A high proportion of patients who add less than one-half pound per week in body weight will gain

more available water than can be accounted for by the weight change. Among patients adding weight more rapidly, a small proportion show such marked disparity between water and weight gains.

Evaluation of Test

Unfortunately there is no known way to select in advance patients whose pregnancies will be complicated by toxemia. The determination of extracellular water, at the proper time in late pregnancy, is only a very short step in that direction. In the present series the test has enabled us to pick out 59 per cent of the "pre-toxic" patients but, as pointed out above, more frequent measurement of the available water would improve this percentage. This selection of "pre-toxic" patients does not seem very specific inasmuch as 4 out of 5 of them do not develop the classical syndrome of pre-eclampsia. (In this series two-thirds of the patients had been put on low salt diets as soon as the excessive water was found: this, it is to be hoped, may have occasionally prevented the appearance of hypertension, proteinuria, edema, etc.)

It would appear from Table V that the test is of very little utility in about one-fourth of all patients, i.e., those whose blood pressures have consistently been less than 110/70. In this group of patients, the incidence of excessive water is low, and very few develop toxemia. In the patients with higher levels of usual blood pressure, the measurement of extracellular water does make a partial separation of the "pre-toxic" patients, although a normal test is no guarantee against toxemia. As a single criterion for selecting "pre-toxic" patients, the trend of the blood pressure would seem nearly as reliable as the measurement of the available water, but if both factors are considered together, a much more reliable prognosis may be made.

Apart from the time involved, the cost of a single measurement of available water is about 2.2 cents. One worker can do 20 to 25 patients a day, including everything from explaining the test to patients and administering the thiocyanate through the collection of blood and urine, to the chemical analyses and arithmetic.

Summary and Conclusions

1. Measurements of thiocyanate-available water (roughly equivalent to extracellular water) were made in 1,388 women in the last ten weeks of pregnancy. Two or more determinations were made in 552 of these patients.

2. The incidence of abnormally increased available water was 19.96 per cent.

3. The incidence of pre-eclampsia was 6 times as great in women with excessive available water as in those with normal water. This difference could have been augmented by more frequent measurements of water.

4. No correlation could be found between serum proteins and the incidence and degree of abnormality of excessive available water. How-

ever, when excessive available water and lowered serum proteins were found together, there seemed to be an increased predisposition to pre-eclampsia.

5. No definite correlation was found between hemoglobin levels and the incidence of excessive available water.

6. The Rh factor seemed to bear no relation either to the incidence of excessive available water or to toxemia.

7. Women with a history of toxemia in a previous pregnancy had a greatly increased incidence of excessive available water, even though they may not have developed a recurrence of hypertension.

8. The incidence of excessive available water rose with increase in body weight. Heavier women with excessive water showed an increasing incidence of toxemia which was not found when the water was normal.

9. Total weight gain until the time of the test did not have any effect upon the incidence of excessive available water or of toxemia unless the weight gain exceeded 30 pounds.

10. The rapidity of weight gain bore no relation to the incidence either of excessive available water or of toxemia until the gain exceeded 4 pounds per week.

11. The rate of weight gain subsequent to the test was somewhat increased in patients who had abnormally increased available water. From this, and from 9 and 10 it would appear that measurement of available water is a better indicator of developing toxemia than is weight-taking.

12. Spontaneous variability in blood pressure did not affect the incidence of excessive available water. If the variation exceeded 20 to 25 mm. Hg in the systolic, the incidence of toxemia was somewhat increased in patients both with normal and with excessive available water.

13. As the usual level of blood pressure increased, there was a rise in both the incidence of excessive available water and the incidence of toxemia. This did not apply in cases of chronic hypertension, where the incidence of excessive available water was about 17 per cent.

14. In women who developed pre-eclampsia, the average interval of time from the measurement of available water to the appearance of hypertension was four weeks if the water was abnormal and six weeks if the water was normal. In a few cases, water retention preceded hypertension by as much as ten weeks.

15. The rate of gain in available water averaged about 250 to 300 ml. per week toward the end of pregnancy, if dietary salt was not restricted. This gain in water tended to be maintained regardless of weight change.

16. From the disparity between available water gain and weight gain in the normal patient, and between available water loss and weight loss on low dietary salt intakes, it was suggested that intracellular water may normally shift out into the interstitial spaces as pregnancy approaches term.

17. An evaluation of the measurement of available water was made.

a. In the present series, 59 per cent of "pre-toxic" patients were picked out by the test. This percentage could have been improved by more frequent measurements of the available water.

b. The test was not specific, inasmuch as 80 per cent of the patients showing excessive available water did not develop pre-eclampsia.

c. Patients with blood pressures consistently below 110/70 showed a low incidence of excessive available water, and seldom developed toxemia. This fact indicated that the test was of little use in about one-fourth of all patients.

References

1. Waters, E. G.: Am. J. Obst. & Gynec. 43: 826, 1942.
2. Chesley, L. C., and Chesley, E. R.: Ibid. 42: 976, 1941.
3. Chesley, L. C.: J. Biol. Chem. 140: 135, 1941.
4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. II. Methods, Baltimore, 1932, Williams and Wilkins, pp. 533 and 602.
5. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, Philadelphia, 1931, P. Blakiston's Son & Co., p. 449.
6. Goudsmit, A., and Louis, L.: Am. J. M. Sc. 203: 914, 1942.
7. Strauss, M. B.: Am. J. Obst. & Gynec. 38: 199, 1939.
8. Peters, J. P., and Eisenman, A. J.: Am. J. M. Sc. 186: 808, 1933.
9. Levine, P., Vogel, P., Katzin, E. M., and Burnham, L.: Science 94: 371, 1941.
10. Matthews, H. B., and Der Brucke, M. G.: J. A. M. A. 110: 554, 1938.
11. Browne, F. J.: J. Obst. & Gynaec. Brit. Emp. 40: 1160, 1933.
12. Thomson, K. J., Reid, D. E., and Cohen, M. E.: Am. J. M. Sc. 198: 665, 1939.
13. Dieckmann, W. J.: Am. J. Obst. & Gynec. 41: 1, 1941.
14. McPhail, F. L.: West. J. Surg. 47: 306, 1939.

Spoto, Pompeo: Labhardt's Subtotal Colpoperineocleisis, Ginecologia 6: 243, 1940.

The author describes, with semischematic drawings, the operative treatment developed by Labhardt and used in the surgical correction of vaginal and vagino-uterine prolapse cases. A descriptive connotation for the surgical procedure is "subtotal colpoperineocleisis." The operation is best suited for those elderly patients who have lost their sexual functions.

The surgical procedure is easily carried out under local anesthesia and would appear, according to the author, superior to other and similar operative methods. The primary operative mortality in 171 cases, reported by Labhardt in 1934, was 1.7 per cent, while in 308 cases, up to July, 1939, the mortality rate was 3.9 per cent. The principal cause of death was pulmonary embolism.

A cure of the prolapse condition was effected in 93.5 per cent of the 308 cases. Sixteen patients had a recurrence of their prolapse, and of these, 8 were reoperated upon successfully.

Spoto reviews and compares the operative methods and results of other authors to those obtained from the Labhardt series.

CLAIR E. FOLSOME

CYCLIC VARIATIONS IN THE CERVIX OF THE GUINEA PIG

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CLOSELY coordinated cyclic changes in various structures of the female genital tract have been clearly demonstrated in the past. This has been shown to be true in animals and in the human being. In the past decade, much has been added to our knowledge regarding changes brought about by hormonal influence on genital structures. Contributions dealing with the physiology of the cervix, however, are few in number. In this report are presented our findings regarding the cyclic changes in the guinea pig cervix, which possibly bear a relation to the human subject.

In a discussion of the estrus cycle in the mouse, Allen[1] makes very little reference to the changes in the cervix. Hammond,[2] in 1927, and Cole,[3] in 1930, described a definite series of changes in the cervix of the cow. Grant,[4] and Cole and Miller[5] have described structural changes in the cervix of the ewe. In 1932 Westman,[6] studying the cervix of the monkey, observed relatively narrow cervical glands in the early part of the cycle, and after ovulation noted dilatation of the glands accompanied by a pronounced secretion from the tall epithelium.

Stieve,[7] in 1927, believed that the cervical epithelium was never in a dormant state. He observed that the cervical glands became larger before menstruation and regressed following the flow. In a study embracing a group of normal patients, presented in a series of papers, Wollner[8-10] found evidence of a definite cycle in the human cervix. The most characteristic changes occurred in the epithelial elements, namely their destruction at the onset of menstruation, followed by rapid regeneration, proliferation and finally secretory activity after the interval period. He was able to correlate this with the cyclic changes of the endometrium.

The first detailed study of cyclic changes in the guinea pig was made by Hartmann and Olbers[11] in 1931. In a series of 36 animals, they found pronounced variations during the estrus cycle. According to these authors, during the diestrus period, the cervical folds are covered with a single layer of columnar epithelium, the folds themselves consisting of a thick nonedematous stroma. The nuclei of the epithelial cells are basally situated and are quite close together. At the beginning of proestrus the layers increase in number, the nuclei shift to the center of the cells, the folds increase in number, and the vessels become congested. In estrus the nuclei disappear, the epithelium separates and is cast off. The stroma during estrus is less dense, the deeper epithelial layers undergoing autolysis with the formation of vacuoles. The whole layer eventually desquamates, following which the fold production begins to decrease. At the beginning of diestrus a simple cuboidal epithelium

is present, covering plump and somewhat edematous folds. A regenerating epithelium is also noted. From the simple cuboidal epithelium a single layer of columnar epithelium develops, beginning during diestrus and remaining until proestrus.

In a most comprehensive work, covering a large series of investigative studies in the guinea pig and human subject, Sjövall[12] has arrived at the definite conclusion, that a clear-cut cyclic phenomenon is present in the cervix. In studying the cyclic changes in the human being, Sjövall found that, during the menstrual cycle, rhythmic changes were evident. During the proliferative phase of the endometrium, an increasing proliferation of the cervical epithelium takes place. Due to a considerable increase in the number of papillary excrescenses, the contour of the superficial epithelium and the glandular epithelium becomes more and more irregular. The proliferation reaches its peak at the time of ovulation and thereafter diminishes, finally ceasing at the end of the secretory phase. The proliferative phenomenon is not seen shortly before, during, and after menstruation.

In Sjövall's series of 52 guinea pigs. he noted a very definite cycle, characterized by distinguishable histologic alterations in the cervix, which were coordinate in most cases with the cyclic variations in the vaginal mucosa and endometrium. Following a modification of the classification of Stockard and Papanicolaou,[13] he divided the estrus cycle into five phases, with a subdivision of Stage I into three parts. He concluded that shortly before and during estrus, marked proliferation with abundant formation of folds took place. A great increase in the number of mucus-secreting cells and an increase in secretion of mucus occurred in the cervix. In the lower portion of this structure, proliferation of an epithelial layer situated beneath the mucous layer, was noted. Cornification and desquamation also were evident. At the end of the estrus phase, leucocytes migrated through the mucous membrane and soon this layer reverted to an indifferent type, with low epithelium, which was characteristic of the diestrus phase. In the upper portion of the cervix, the changes were not as characteristic and no evidence of desquamation was noted.

Material*

Normally cycling animals were used in this investigation. Carefully selected virgin female guinea pigs were followed from one to three months after maturity had been reached. Fifty-three animals were used for this study. Vaginal smears were taken during various stages of the cycle by means of a wire loop moistened in normal saline solution. The vaginal smear was stained with hematoxylin and eosin, after being air dried. Although the Shorr stain was tried, there was no particular advantage in its use. Animals were sacrificed at various stages, the genital organs immediately removed and fixed in 10 per cent formalin, Bouin's solution, or 100 per cent alcohol. Longitudinal sections or several transverse sections were made of the vagina, cervix, uterus, and ovaries, blocked in paraffin, sectioned, and then stained with hematoxylin-eosin, Best's carmine stain, or mucicarmine.

For designation of the various stages of estrus and diestrus, in relation to the cyclic changes in the vagina, we have adopted Sjövall's classification, which of course is a modification of the classification set forth by Stockard and Papanicolaou. Estrus is divided into three stages, namely, I, II, and III. Diestrus is called Stage IV, and proestrus is symbolized as V. Stage I, or early estrus, is further subdivided into Ia, Ib, and Ic, according to well-defined histologic findings. The stages may be summarized as follows, according to findings in the vaginal smear:

Ia: Intact mucous cells with intact nuclei. No evidence of degeneration
Ib: Vacuolated mucous cells with pyknotic or fragmented nuclei.
Ic: Anuclear cells.
II: Cornified nucleated cells.
III: Flattened epithelial cells and *leucocytes*.
IV: Leucocytes and occasional epithelial cells.
V: Intact mucous cells and leucocytes.

Gross Changes

During diestrus, very little secretion is present in the vagina and cervix. The entire genital tract is relatively atrophic. In proestrus and early estrus, there is an abundance of tenacious mucus in the vagina and lower cervix. This changes to a thinner consistency in late estrus and is associated with many small white clumps, made up of cells. The genital structures undergo gross hypertrophy associated with evident softening and congestion.

Histologic Changes

Rather profound and characteristic alterations are noticed in the cervix. During diestrus, Stage IV, the lower portion of the cervix is comprised of a relatively thin mucosa, composed of two layers, the deeper portion consisting of several layers of squamous epithelium, sometimes designated as the basal layer. Covering the latter, is another layer made up of one or more rows of cuboidal or columnar mucus-containing cells, with dark-staining basal nuclei. The relatively few folds of epithelium present during this stage are short and blunt. Several leucocytes are usually noted in the epithelium and on the surface. The upper cervix discloses relatively simple glands, lined by low columnar or cuboidal cells containing a small amount of mucus, and compact dark-staining nuclei, which are usually basally situated. A few scattered leucocytes are usually present. Practically no secretion is encountered during this stage. Usually many vacuolated areas are present in the epithelium. The vaginal mucosa presents a picture very similar to the lower portion of the cervix. The uterus during this stage consists of a rather atrophic layer of endometrium and a dense compact stroma, with scattered leucocytes.

A very marked change occurs from about the fifteenth to the seventeenth day of the cycle. During this proestrus stage (Stage V), conspicuous evidence of proliferation is present. The basal epithelium of the lower cervix shows marked hyperplasia with many mitotic figures present in the deeper layers. Hyperplasia of the mucous layer occurs to a very marked extent while the cells fill up with mucus and actively secrete the substance in the lumen. There are many areas present where it appears as if the basal epithelium has become trabeculated, and here one gains the impressian that a transition of the epithelium is occurring,

from squamous-like cells to mucous cells. In the cranial portion of the cervix, the glands gradually enlarge and evidence of beginning fold formation and tufting can be seen. The cells have changed from cuboidal to columnar and now contain basal nuclei and an increased amount of mucus. A small amount of this material can be noted within the glands themselves.

An equally intense change occurs in the vagina during Stage V. The squamous epithelium proliferates rapidly, showing mitotic figures in the deeper layers, and cornification in the upper layers. The covering layer of mucous cells undergoes marked hyperplasia and fold formation. The endometrium shows a corresponding hyperplasia and hypertrophy, although not as striking as in the cervix and vagina.

During the earlier part of estrus, the process is a continuation of the marked proliferative changes noted in the proestrus phase. In Stage Ia, the lower cervix follows closely the development of the vagina. Hyperplasia of the basal layer continues here with mitotic figures readily found. The mucous layer rapidly proliferates covering the basal layer.
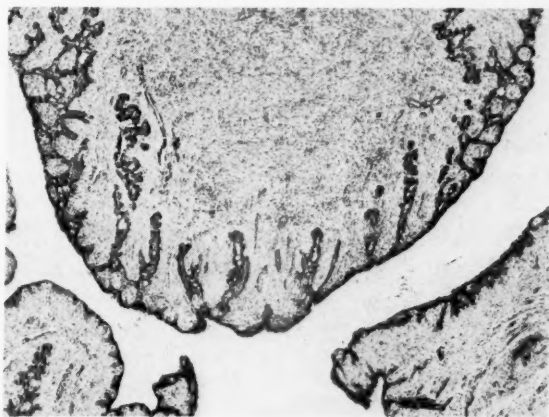
Fig. 1.—Low power photograph of lower portion of cervix and vagina during Stage IV (diestrus). Note thin mucosa.

In some areas there occurs a piling up of the mucous cells with beginning tuft formation. No evidence of desquamation is encountered, but active secretion makes its appearance. Leucocytes are conspicuously absent. In the upper cervix the glands have shown an increase in size and complexity, and active secretion is present. The cells are quite tall, many are tremendously ballooned out, due to the rapid increase in the amount of intracellular mucus. The darkly stained round nuclei are situated close to the base of the cell. Tufting has become more conspicuous. The vaginal mucosa becomes thicker, a marked hyperplasia of the epithelium occurs with mitotic figures still prevalent. Cornification in the upper layer, is much better developed than in proestrus. The mucous cell layer is quite thick, with many desquamated mucous cells present in the lumen. These cells contain well-formed small dark intact nuclei and show no evidence of degeneration. A very characteristic difference between proestrus and Stage Ia is the disappearance of leucocytes in the latter stage. The endometrium also shows alterations, the endometrial cells have become taller, and numerous mitotic figures are to be found. Practically no white blood cells are present. The stroma shows proliferation and edema.

Proliferation continues in Stage Ib. The mucous cells which continue to be cast off from the vaginal mucosa, have undergone degenerative changes, such as vacuolization of the cytoplasm, and fragmentation of the nuclei. Cornification also shows some increase. In the lower cervix, the mucous cell layer has assumed rather marked proportions by virtue of an increase in the number of layers, and by exaggeration of the tufts and folds. Many cells have become separated and cast off into the lumen.
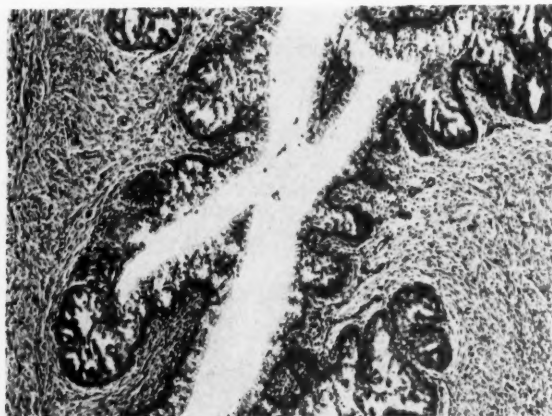
Fig. 2.—Low power photograph of lower part of cervix during Stage V (proestrus).
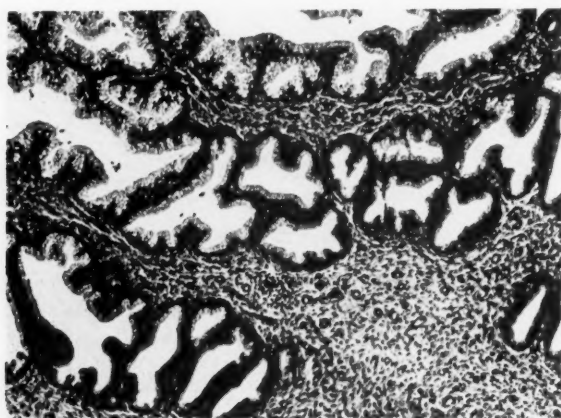
Fig. 3.—Low power view of upper cervix, Stage V (proestrus), showing simple glands.

The basal layer remains hyperplastic although mitotic shapes are no longer in evidence. The glands in the upper cervix are now tremendously enlarged with multiple tufts and excrescenses. The cells are very tall and protuberant, with active secretion well marked. The growth is so great in many cases that the glandular lumina are filled by the volume of the cells. The endometrium is similar to that noted in Stage Ia.

During Stage Ic, cornification reaches its peak in the vagina and cervix, with desquamation of the anuclear cornified cells. The lower cervix shows considerable increase in the prominence of the cornified

layer.   Here there is a casting off of the mucus and also the anuclear cells, but no further hyperplasia is noted.   The glands have very much the same appearance as in Stage Ib.   No significant alteration has occurred in the endometrium, other than that already noted in Stages Ia and Ib.

Stage II, according to Sjövall and others, is the interval immediately preceding ovulation.   Examination of the smear reveals well-outlined round, polyhedral, or occasionally, some flattened cells with distinct but
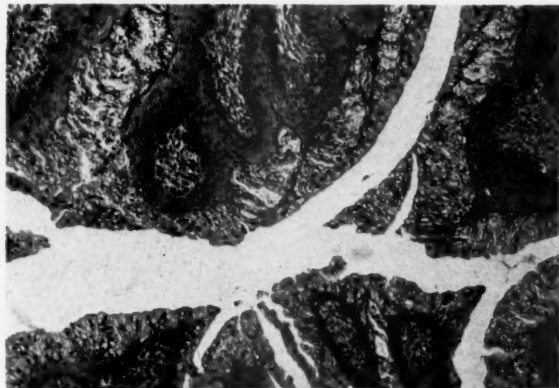
Fig. 4.—Lower portion of cervix during Stage Ia.   Note hyperplasia of basal layer and mucous cell layer (low power).

Fig. 5.—Stage Ib showing lower portion of cervix with marked hyperplasia of epithelial layers (low power).

pale intact nuclei.   No leucocytes are present.   In the lower cervix, distinct desquamatory changes occur, which are more impressive than in previous stages.   Usually there is a separation between the mucous cell layer and the first or second layer of the basal cells, so that the desquamated cells consist of mucous cells plus basal cells.   Leucocytes again are absent.   In a few animals early degenerative changes may be noted in the epithelium, but this is not the rule.   In the upper cervix, the glands are still quite irregular, show considerable tufting, and con-

tain variable amounts of mucus. A rather striking change now occurs in the position of the nuclei of the mucous cells. Hitherto, they were flattened against the base of the cell, but now they show a distinct tendency to be centrally situated. Many cells had shown this tendency in earlier phases, but the change is more pronounced during this stage.
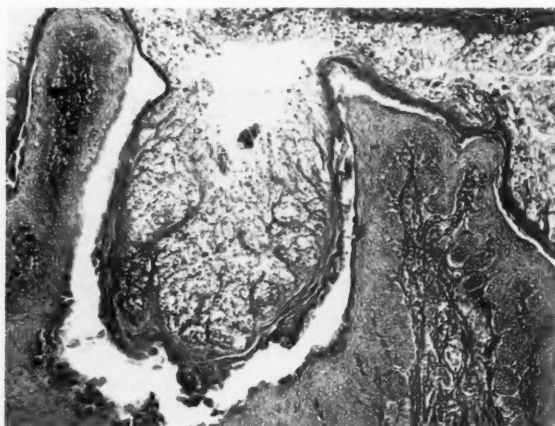
Fig. 6.—Lower cervix (low power) demonstrating desquamation of mucous cells. Layer of cornification between the basal cell and mucous cell layers is quite evident.
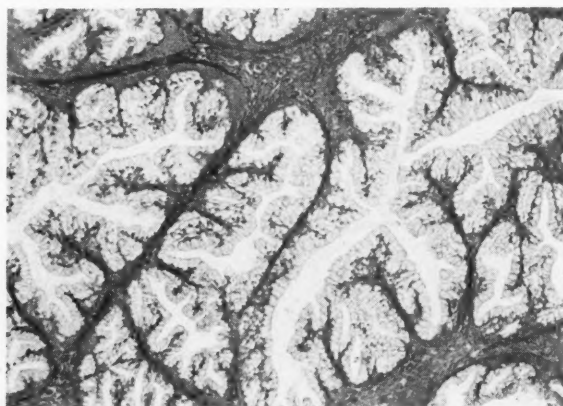
Fig. 7.—Complex glands with tuft formation, noted in upper cervix during Stage Ic (low power).

Occasional formation of vacuolated spaces is encountered, but this is by no means characteristic. The vaginal mucosa is somewhat thinner, since the mucous cells and cornified layer have for the most part been cast off. The top layer of the epithelium consists of flattened or round cells, many of which have been cast off and are found in the lumen. The endometrium shows practically no change in cellular appearance, with the exception of leucocytic infiltration beneath the epithelium and in the glands.

Following ovulation, Stage III, or late estrus, is ushered in. The vaginal smear consists of flattened cornified cells plus leucocytes. The

characteristic changes noted in this phase are degeneration and leucocytic infiltration. The basal epithelium of the cervix is thinner than in previous stages of estrus. Many vacuolated areas are present in both the basal and mucous cell layers. Throughout the basal layer, many of the cells undergo a peculiar degenerative change. The cells become quite large, in fact many appear like giant cells. The cytoplasm changes

Fig. 8.—Low power photograph of lower cervix during Stage II (midestrus) illustrating desquamation of basal cells.
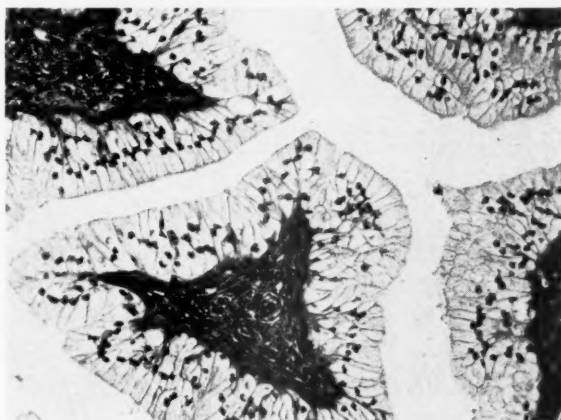
Fig. 9.—High power photograph showing centrally situated nuclei of the mucous cells in the upper cervix, during Stage II.

its staining properties, taking on a pinkish or orange color, while the nuclei become fragmented. Soon an area about these cells becomes vacuolated, and often the degenerated cells completely disappear, leaving spaces. Sjövall has not mentioned this degeneration of the cells, which we noted as a very constant and conspicuous change. Later, due to the great number of these vacuoles, the mucosa takes on a "punched-out" appearance. In some areas where degeneration seems to be at its peak, actual necrosis is seen. The leucocytes increase in number and are scattered throughout the basal and mucous cell layers.

The rather irregular glands of the upper cervix show active secretion, although diminished in amount in comparison to that noted in the previous stages. The nuclei for the most part are still centrally located. Degenerative changes and leucocytes, although present, are not nearly as great as in the lower cervix. However, the vacuolated areas are quite impressive. The vaginal mucosa is much attenuated and only a few layers of epithelium still persist. The upper layer consists of flattened cells, and throughout the tissue many white blood cells have made their appearance, with the greatest concentration toward the lumen surface. The endometrium shows a further increase in the number of leucocytes. Degenerative changes are quite conspicuous as evidenced by loss of cell detail and nuclear degeneration. A few cases showed areas of hemorrhage, although this was by no means the rule. From this phase there is a fairly rapid degeneration and the full picture of Stage IV is then encountered.
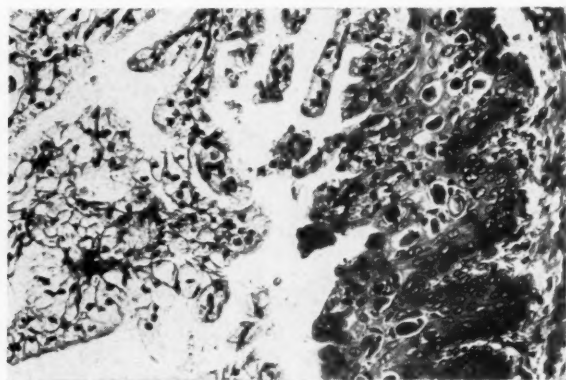
Fig. 10.—Marked degeneration in the lower cervix in Stage III (late estrus). Note the vacuoles containing the degenerated epithelial cells (high power.)

Comment

While the cyclic changes just described represent the characteristic picture, as in all biologic phenomena, variations from the "normal" were encountered. In this series, the length of the cycle varied from fifteen to eighteen days. The duration of estrus as determined by the opening and closing of the vagina, varied from two to four days. Stages I, II, and III did not bear a direct relation to the corresponding three days of the average estrus phase. By examining Table I, it is noted that most of the animals, presenting Stage III, were found in this phase on the second day of estrus. Seven guinea pigs showed the lack of complete correspondence of the stages in the various parts of the genital tract. Two more showed variation of the endometrium only, thus making a total of nine in this series which did not show characteristic coordinated alterations.

Considerable variation in the number and distribution of leucocytes in late estrus was noted. Some of this was undoubtedly due to the

period in Stage III when the animal was sacrificed. For instance, in the early part of this stage, relatively few white blood cells are present, while later in the same phase more leucocytes are evident in the tissues. Occasionally, a few leucocytes persist in Stage Ia. Two animals showed

TABLE I

NO.	DAY KILLED	VAGINAL SMEAR (STAGE)	VAGINA (STAGE)	CERVIX (STAGE)	UTERUS (STAGE)
1	Second day estrus	II	II	II	II
2	?	III	III	III	III
3	First day estrus	III	III	III	III
4	Second day estrus	Ic	Ic	Ic	II
5	First day estrus	Ib	Ib	Ib	I
6	First day after estrus	Closed	IV	IV	IV
7	First day after estrus	Closed	IV	IV	IV
8	Second day estrus	III	III	III	III
9	Second day estrus	III	III	III	III
10	Second day diestrus	Closed	IV	IV	IV
11	First day estrus	II	II	II	III
12	Third day diestrus	IV	IV	IV	IV
13	?	Closed	IV	IV	IV
14	Eighth day diestrus	Closed	IV	IV	IV
15	Second day estrus	III	III	III	III
16	10th day diestrus	Closed	IV	IV	IV
17	Seventeenth day (proestrus)	V	V	V	III
18	First day estrus	Ia	Ia	Ia	I
19	Fifteenth day (proestrus)	V	V	V	V
20	Second day estrus	Ic	Ic	Ic	I
21	Fifteenth day (proestrus)	V	V	V	V
22	Second day estrus	III	III	III	III
23	First day estrus	Ib	Ib	Ib	I
24	Fifteenth day (proestrus)	V	V	V	V
25	Fifteenth day (proestrus)	V	Ia	V	V
26	First day estrus	Ia	Ia	Ia	I
27	Second day estrus	II	II	III	III
28	Second day estrus	II	II	II	II
29	Second day estrus	II	Ib	Ib	I
30	Sixteenth day (proestrus)	V	II	II	I
31	First day estrus	Ia	Ia	Ia	I
32	Second day estrus	III	III	III	III
33	First day estrus	Ia	Ia	Ia	I
34	First day estrus	Ia	Ia	Ia	I
35	First day estrus	II	II	II	II
36	Third day estrus	III	III	III	III
37	Second day estrus	III	III	III	III
38	First day estrus	V	V	V	V
39	Second day estrus	Ic	Ic	Ic	I
40	Third day estrus	III	III	III	III
41	First day estrus	Ia	Ia	Ia	I
42	Second day estrus	III	III	III	III
43	First day estrus	Ib	Ic	?	I
44	First day estrus	Ia	Ia	Ia	I
45	Second day estrus	III	III	III	III
46	Eleventh day diestrus	Closed	IV	IV	IV
47	Second day estrus	III	Ib	III	III
48	First day estrus	Ia	Ia	Ia	I
49	Second day estrus	II	II	II	II
50	Second day estrus	II	II	II	II
51	Eleventh day diestrus	IV	IV	IV	IV
52	First day diestrus	IV	IV	IV	IV
53	Second day estrus	II	II	II	II

evidence of proliferation in early diestrus, this being particularly true in the endometrium. In this series, the number of animals encountered in each stage is shown in Table II.

TABLE II

STAGES	NO. OF ANIMALS
Ia	8
Ib	2
Ic	2
II	6
III	12
IV	10
V	4
Inconclusive	9
Total	53

Our sections stained for glycogen were a keen disappointment. We expected to find a cyclic variation in respect to the glycogen content of the epithelial cells, but very little of this material could be demonstrated.

Although the most characteristic changes during the cycle were found in the cervical mucosa, there was a notable cyclic alteration in the stroma and blood vessels. During diestrus, the stroma is quite dense, with no evidence of congestion. There is an increase in both stroma cells and in the degree of vascularity in proestrus. This congestion and stromatous increase reaches its peak during early estrus with moderate edema also conspicuous at this time. These changes begin to show a definite decrease beginning with late estrus.

Sjövall did not detail the time of migration of the nuclei to a central location in the mucous cells, although we found this to occur with a high degree of consistency, namely during Stages Ic and II. This central location of the nuclei continues in Stage III, and often persists into early diestrus.

During Stage III, Sjövall stated that many leucocytes appeared in the epithelium of the cervix, as large round bodies. Leucocytes invariably do make their appearance during this phase, but we believe that the large round bodies, described by Sjövall as leucocytes, are actually degenerated epithelial cells. Some of the animals showed localized areas of simple necrosis, a further evidence of profound degenerative changes.

Summary

In our series, we have satisfied ourselves that in the guinea pig, a definite recognizable cyclic change occurs in the cervix, during the estrus cycle. These alterations follow very closely the variations present in the other parts of the genital tract, especially in the vagina. Emphasis must be placed on the fact, that the most characteristic findings are present in the lower cervix, although they are by no means

absent in the upper part. In spite of the fact that the ovaries were examined grossly and microscopically, no attempt was made to correlate ovulation and corpus luteum formation with variations in the cervix, because of the technical handicaps incidental to making serial sections of the ovaries. We found gross inspection of the ovaries inadequate for proper correlation. We feel that the cyclic changes are probably dependent on the hormonal cycle. Sjövall has shown this to be true in part, although he believed that all the variations could be explained on the basis of estrin alone.

We may summarize the findings in the cervix during the various stages as follows :

ESTRUS

Stage Ia.—Lower cervix: Hyperplasia of the basal epithelium and the mucous cell layer. Absence of white blood cells.

Upper cervix: Proliferation of the glandular epithelium and an increase in the complexity of the glands. Absence of leucocytes.

Stage Ib.—Lower cervix: Hyperplasia of both layers, with beginning desquamation of the mucous cells.

Upper cervix: Increase in the size of the glands, and further tufting of the glandular epithelium.

Stage Ic.—Lower cervix: Definite cornification. Further desquamation of mucous and anuclear cells.

Upper cervix: Similar to Stage Ib.

Stage II.—Lower cervix: Distinct desquamation of mucous cells and nucleated basal cells.

Upper cervix: Shifting of the nuclei of the epithelial cells toward the center of the cell.

Stage III.—Lower cervix: Leucocytic infiltration into the mucosa and lumen. Definite degenerative changes.

Upper cervix: Degenerative changes. Conspicuous central location of nuclei of glandular epithelial cells. White blood cell infiltration.

DIESTRUS

Stage IV.—Lower cervix: Persistent leucocytosis. Further degenerative changes. Atrophy of basal and mucous cells to the resting type (low columnar or cuboidal cells).

Upper cervix: Similar changes as noted in lower cervix. The glands are smaller, and the vacuoles are quite prominent in many cases.

PROESTRUS

Stage V.—Lower cervix: Evidence of proliferation of basal and mucous cells. Leucocytosis diminishes. Many mitotic figures are present in the basal epithelium.

Upper cervix: The glands become larger and slightly more irregular. Epithelial cells increase in size.

Conclusions

Evidence has been presented to show that a definite cycle with characteristic changes is present in the guinea pig cervix.

In a series of 53 animals, 44 showed changes in the cervix which were coordinate with the normal rhythmic alterations found elsewhere in the genital tract.

References

1. Allen, Edgar: Am. J. Anat. **30:** 297, 1922.
2. Hammond, J.: Reproduction in the Cow, London, pp. 93-94, 1927.
3. Cole, H. H.: Am. J. Anat. **46:** 261, 1930.
4. Grant, R.: Tr. Roy. Soc. Edinburgh **58:** 16, 1934.
5. Cole, H. H., and Miller, R. F.: Am. J. Anat. **57:** 39, 1935.
6. Westman, A.: Acta obst. et gynec. Scandinav. **12:** 282, 1932.
7. Stieve, H.: Das Halsteil der menschlichen Gebarmutter Bau und seine Aufgaben wahrend der Schwangerschaft, der Geburt und des Wochenbettes, Leipzig, pp. 1-150, 1927.
8. Wollner, A.: Am. J. Obst. & Gynec. **32:** 365, 1936.
9. Wollner, A.: Surg., Gynec. & Obst. **64:** 758, 1937.
10. Wollner, A.: Am. J. Obst. & Gynec. **36:** 10, 1938.
11. Hartmann, H., and Olbers, H.: Zentralbl. f. Gynäk. **55:** 1314, 1931.
12. Sjövall, A.: Acta obst. et gynec. Scandinav. **28:** Suppl. 4, 1938.
13. Stockard, Ch. R., and Papanicolaou, G. N.: Am. J. Anat. **22:** 225, 1917.

CEREBRAL COMPLICATIONS OCCURRING IN THE TOXEMIAS OF PREGNANCY*

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THE purpose of this presentation is to emphasize and illustrate some of the serious cerebral complications associated with the toxemias of pregnancy. During a four-year period of study from July 1, 1938, to July 1, 1942, there were 9,693 admissions to the obstetric service; 8,457 patients were delivered, and 1,009 mothers showed clinical evidence of late toxemia of pregnancy. In the group with toxemia, 41 patients had typical eclamptic convulsions; 6 patients developed critical cerebral complications, and there were 7 maternal deaths.

A clinical classification and the maternal mortality rate for the different types of toxemia are given in Table I. In this study, the admission ratio was approximately five colored to one white patient. The common occurrence of hypertensive disease in Negro women probably accounted, in part, for the high percentage of patients with chronic cardiovascular-renal disease complicated by pregnancy. The one death in the group with chronic vascular nephritis was due to cerebral arteriosclerosis with multiple minute hemorrhages. Acute nephrosis following abruptio placentae and a blood transfusion reaction accounted for one

death. Of the four patients who died with eclampsia, two had typical convulsions, and all four showed gross evidence of cerebral hemorrhage.

TABLE I. CLINICAL CLASSIFICATION AND MATERNAL MORTALITY RATE IN 1,009 PATIENTS WITH TOXEMIA OF PREGNANCY

TYPE OF TOXEMIA	NUMBER OF PATIENTS	IN-CIDENCE PER CENT	MATERNAL MORTALITY	
			NO.	PER CENT
Hypertensive cardiovascular disease, mild	160	15.86	0	0
Hypertensive cardiovascular disease, severe	131	12.98	1	0.76
Chronic vascular nephritis	83	8.23	1	1.20
Chronic glomerulonephritis	5	0.50	0	0
Acute nephritis or acute nephrosis	1	0.10	1	100.00
Pre-eclampsia, mild	413	40.93	0	0
Pre-eclampsia, severe	175	17.34	1	0.57
Eclampsia*	41	4.06	4	9.75
Total	1,009	100.00	8	0.79

*Eclampsia with and without convulsions.
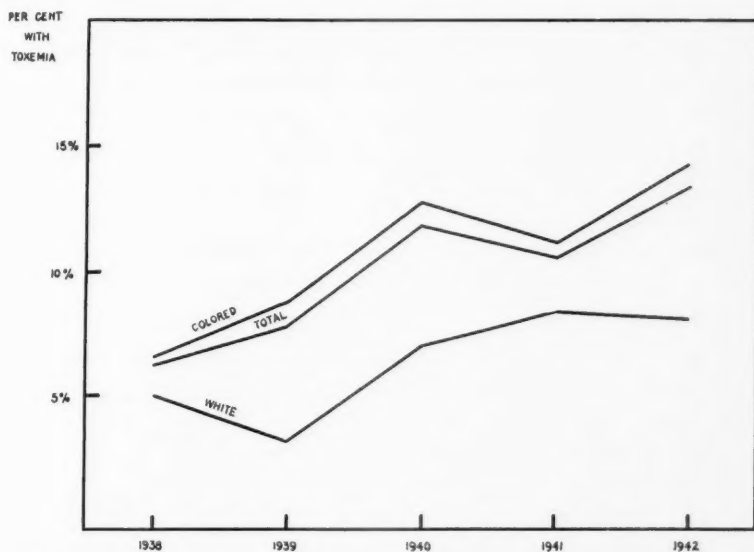
Fig. 1.—Incidence of toxemia occurring in the 9,693 patients hospitalized between July 1, 1938, and July 1, 1942.

In the two remaining cases, the cause of death was uncertain. One patient with severe hypertensive cardiovascular disease, uncontrolled diabetes, and premature labor died a few hours after admission of what was thought to be acute heart failure. The other patient went into labor with a severe preeclamptic toxemia. She died suddenly. The clinical impression was pulmonary embolism. Neither lumbar puncture nor post-mortem examinations were performed on these two patients. The presence or absence of cerebral hemorrhage as a factor in their sudden death was not determined.

During the past four years, the incidence of toxemia at Gallinger Municipal Hospital has increased from 6.52 per cent in 1938 to 13.43 per cent in 1942 (Fig. 1). The increasing incidence of toxemia in our group of patients may be partially explained by the recent migration to

Washington of many women of childbearing age who are undergoing economic and social readjustments and who possibly are not obtaining sufficient prenatal care.

Vascular Changes in the Toxemias of Pregnancy

Knowledge of the cerebrovascular changes in the toxemias of pregnancy may lead to earlier recognition and the prevention of critical intracranial complications. These changes may be classified as follows: (1) arteriospasm, (2) cerebral edema, (3) thrombosis of cerebral vessels, (4) intracerebral hemorrhage due to rupture of cerebral vessels or to rupture of vessels of the choroid plexus, and (5) extracerebral (subarachnoid) hemorrhage.

The cause of arteriospasm in the toxemias of pregnancy is not known. Clinical manifestations of arteriospasm depend upon the cerebral vessels involved, the duration of the spasm, and the degree of tissue anoxia produced. The sequelae of arteriospasm are seldom permanent. If death occurs, it is difficult to demonstrate the cerebral pathology.

The same factors which cause edema elsewhere in the body of patients with toxemia of pregnancy give rise to cerebral edema. Edema of the brain may lead to convulsions, coma, paralysis, and in some instances to death. The outstanding post-mortem finding in cerebral edema is the "wet brain" of serous apoplexy.

Clinically, thrombosis of a cerebral vessel may be difficult to distinguish from an intracerebral hemorrhage which has not extended beyond the brain tissue. In both instances the spinal fluid will be clear. Thrombosis is more likely to occur in the patient who has chronic vascular disease of hypertensive or syphilitic origin.

Intracranial hemorrhage is a relatively frequent and extremely significant complication of eclampsia. Factors which may lead to rupture of cerebral vessels in the toxemias of pregnancy are: (1) Changes in arteriocapillary walls due to spasm, edema, and ischemia; (2) increased vascular tension associated with eclamptic convulsions; (3) the chronic vascular changes of persistent hypertension and of syphilis; and (4) congenital aneurysm. Grossly bloody spinal fluid is diagnostic of a hemorrhage which has either originated in the meninges or has extended from the brain into the ventricles or subarachnoid space. If the cerebral hemorrhage is sudden and extensive, all motor pathways may be blocked, preventing convulsions.

Literature

In the literature, cerebral complications of the toxemias of pregnancy have been described under various headings.

Eclampsia With Convulsions and Cerebral Hemorrhage.—In 1881, Schauta found cerebral hemorrhage in 10 out of 90 eclamptic patients at autopsy. Prutz, in 1892, stated that 3 out of 22 brains examined showed cerebral hemorrhage. Schmorl, in examining 73 cases of fatal

eclampsia, found small pinhead-sized hemorrhages, or areas of necrosis in 58, and gross hemorrhage in only 1. Dieckmann states that Jaffe found 5 patients with massive cerebral hemorrhage in 8 autopsies and edema of the brain in the remaining 3. Rheindorf reported cerebral hemorrhage in 10 per cent of deaths due to eclampsia. Kosmak, in his monograph on toxemias, states that some degree of cerebral hemorrhage is found at autopsy in most eclamptic deaths.

Additional reports of cerebral hemorrhage in eclampsia have been recorded by the following authors: 7 cases by Meyer-Wirz, 5 by Bouffe de St. Blaise, 3 by Levant and Portes, 2 by Rheindorf, and 1 each by Welch, Carver and Fairbairn, Maygrier and Chevane, Binder, Rhemann, and Liebers.

In 1887, Klebs reported gross hemorrhage of the brain occurring in a patient with acute yellow atrophy of the liver. In 1897, Pfannenstiel described an eclamptic death due to a ruptured cerebral varix.

Cerebral Hemorrhage in Eclampsia Without Convulsions.—In 1907, Slemons reported 9 cases (2 of his own) of eclampsia without convulsions terminating in cerebral apoplexy. In 1911, Schmid reviewed the literature and brought the total of reported cases to 24. In 1927, Caffier reviewed 38 cases. King reported a case of eclampsia without convulsions complicated by cerebral hemorrhage and analyzed 30 of the 44 cases previously reported. In 10 of the 30 cases, the diagnosis was missed until autopsy. Of 23 brains examined, 2 were normal, 2 were ischemic, 10 showed punctate hemorrhages, and 9 showed massive hemorrhage. In 1941, Abbott reported a patient with toxemia of pregnancy in which cerebral hemorrhage was diagnosed. The intracranial clot was removed on the second post-partum day. Except for a residual homonymous hemianopsia, the patient made a remarkable recovery.

Paralysis in the Toxemias of Pregnancy.—In 1904, v. Hoesslin made an extensive survey of all types of paralysis occurring in pregnant women. In his article he reviewed 32 cases of paralysis associated with the toxemias of pregnancy. Schwanen, in 1934, reviewed 47 cases which included those previously reported by v. Hoesslin, 12 additional cases from the literature, and 3 of his own. A search of the available literature revealed reports of additional cases of Bouffe de St. Blaise, Mondy, Cronson, Barrett and Harger, Liebich, Henriet, Dieckmann, Hajkis, and McMann which were not included in Schwanen's article. McMann's report described an eclamptic patient who developed a monoplegia which lasted only five days and was attributed to arteriospasm. With the addition of a case to be presented below, 57 reports of paralysis in the toxemias of pregnancy are available for analysis. Forty-six patients had hemiplegia and 11 had monoplegia. There were 27 patients with and 30 without convulsions. In the entire group there were 20 deaths, giving a mortality rate of 35 per cent.

Eclampsia With Convulsions and Cerebral Hemorrhage

CASE 1.—L. T., colored, unregistered, gravida vii, aged 30 years, approximately thirty weeks pregnant, was admitted Aug. 5, 1941, in deep coma. Her first pregnancy terminated as an abortion. She subsequently gave birth to five living infants, each pregnancy being complicated by hypertension and albuminuria. For five weeks prior to admission, headache and edema of the extremities had been present.

The hospital course of this markedly edematous, moderately obese patient is outlined in Fig. 2. Because of fetal heart sounds and fetal activity, an immediate post-mortem cesarean section was performed.

Spinal fluid was grossly bloody in all specimens. Blood urea nitrogen was 20, uric acid 5.7, and sodium chloride 462 mg. per cent. Coffee-colored catheterized urine showed specific gravity 1.014, 4-plus albumin, white and red blood cells, and many granular casts. The coroner released the body without necropsy.
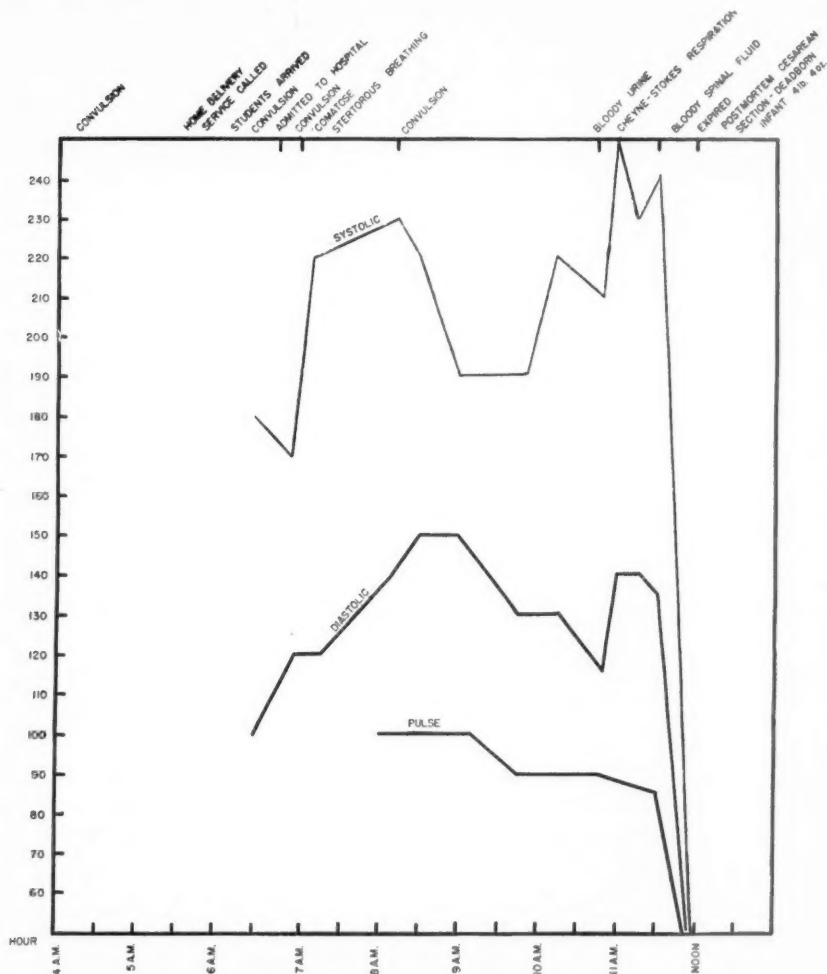
Fig. 2.—(Case 1.)   Eclampsia with convulsions and cerebral hemorrhage.

CASE 2.—E. K., colored, gravida vi, 22 years of age, was admitted on Jan. 20, 1941, complaining of severe headache and amblyopia. At her only prenatal clinic visit, on Oct. 23, 1940, no symptoms or signs of toxemia were noted. About twenty-four hours after the report of a death in the family, the patient had two convulsions. Shortly after admission to the hospital, she had a third convulsion. Hourly blood pressure read-

ings showed the systolic blood pressure ranging between 130 and 180 and the diastolic pressure varying from 90 to 130 mm. Hg. Thirty hours after admission she delivered, spontaneously, a living infant weighing 5 pounds 13 ounces (2,637 Gm.). Following delivery, the pulse became slow and irregular. The blood pressure was maintained at a level of about 140/100. Ninety minutes after delivery, the patient became comatose; blood pressure dropped to imperceptibility, and the pulse became rapid and irregular. Pulmonary edema and gasping respirations developed. The eyes deviated to the left. The pupils became dilated, the right being larger than the left.
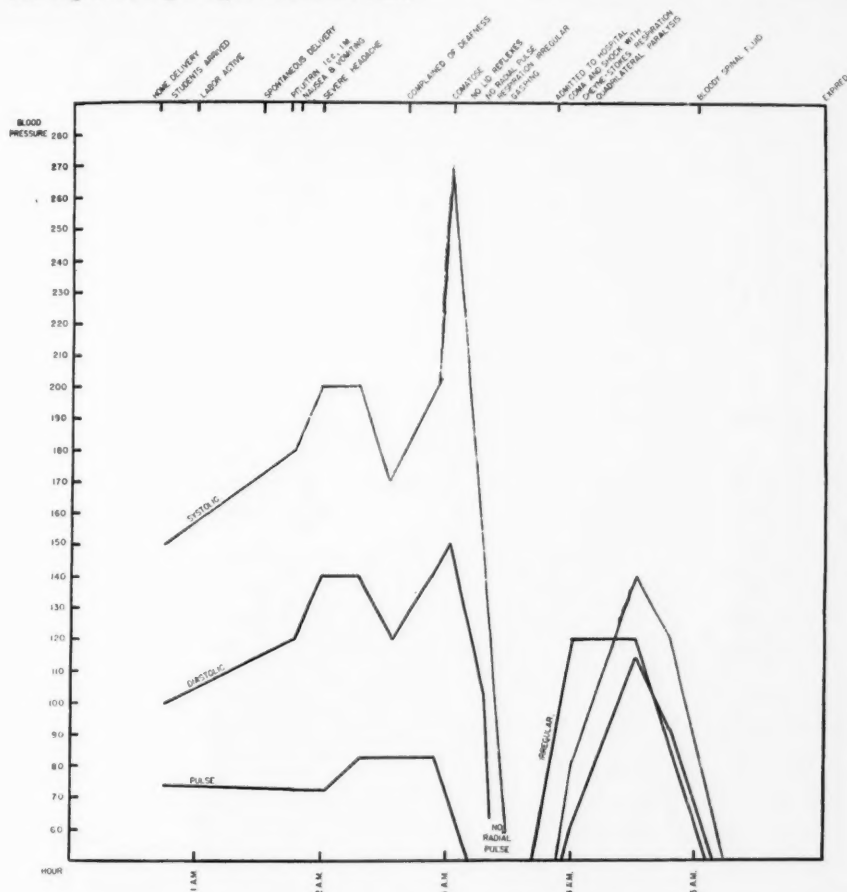
Fig. 3.—(Case 3.) Cerebral hemorrhage in eclampsia without convulsions.

Diagnostic lumbar puncture was productive of grossly bloody spinal fluid in all specimens. Patient died three hours after delivery. Urine showed 3-plus albumin and occasional casts. Permission for post-mortem examination was refused.

Cerebral Hemorrhage in Eclampsia Without Convulsions

CASE 3.—C. M., colored, gravida v, aged 27 years, was admitted from the home delivery service on July 3, 1940, in coma. Prenatal care con-

sisted of one visit to a clinic on June 28, 1940, where it was recorded that she had had scarlet fever in childhood, blood pressure 180/110, and 1-plus albuminuria. Additional history of swollen ankles, scotomas, headache, and vertigo of one month's duration was obtained at the time of delivery.

The patient's terminal clinical course is charted from home delivery and hospital records in Fig. 3. Attention is called to the use of pituitrin in this hypertensive patient. Death occurred two and one-half hours after admission to the hospital.

Fig. 4.—(Case 4.) Eclampsia with atypical convulsions and cerebral hemorrhage.

Spinal fluid was grossly bloody. Blood urea nitrogen was 20, cholesterol 200, and sodium chloride 511 mg. per cent. Urine showed 2-plus albumin, many red and white blood cells, and no casts. At post mortem, the enlarged liver showed diffuse subcapsular hemorrhage as well as gross and microscopic evidence of extensive periportal hemorrhage and necrosis. Hepatic hemorrhage was more pronounced in the right than in the left lobe. The kidneys showed edema and desquamation of the tubular epithelium. The glomeruli were normal. Unfortunately the brain was not examined.

Eclampsia With Atypical Convulsions and Cerebral Hemorrhage

CASE 4.—M. D., colored, unregistered, primipara, aged 25 years, in the twenty-sixth week of pregnancy, was admitted on Feb. 13, 1940, in active labor. Ankle edema had been present for one month. Headache and vomiting occurred on the day of admission. Her mother died in childbirth at 32 years of age. One brother died of cerebral hemorrhage.

The patient's clinical course is recorded in Fig. 4. In addition, ophthalmic examination showed perivascular edema of the left retina and old and recent hemorrhage into the right retina. The stillborn infant weighed 4 pounds 14 ounces (2,211 Gm.). The bloody spinal fluid was under a pressure of 47 mm. Hg.

Blood urea nitrogen was 29, cholesterol 166, icterus index 50, and sodium chloride 528 mg. per cent. Urine showed specific gravity 1.035, 4-plus albumin, hyaline and granular casts.

Important post-mortem findings were limited to the brain, liver, and kidneys. Upon removal of the dura, a flat mass of clotted blood covered both frontal and parietal areas. The right lateral ventricle was filled with a large, firm blood clot. Except for small blood clots in the arachnoid, the basilar portion of the brain appeared normal. Microscopic sections showed frank subarachnoid hemorrhage associated with petechial hemorrhage in the subjacent brain tissue. The liver showed many small areas of periportal focal necrosis. The kidneys showed cloudy swelling of the tubules and vascular congestion.

Pregnancy Complicated by Arteriosclerosis and Multiple Minute Cerebral Hemorrhages

CASE 5.—M. M., colored, gravida vi, para iii, aged 40 years, was admitted on Feb. 2, 1942, because of headache and hypertension complicating a pregnancy of twenty-six weeks' duration. Hypertension had been present with pregnancies in 1928, 1930, and after removal of a ruptured tubal pregnancy in 1941.

Important physical findings were: generalized edema, cardiac enlargement, and typical hypertensive changes in the optic fundi. Bidaily blood pressure recordings ranged from 185/110 to 260/145.

On March 8, 1942, pregnancy was further complicated by partial premature separation of the placenta and a transverse presentation of the fetus. A living infant weighing 3 pounds 15½ ounces (1,800 Gm.) was delivered by classical cesarean section and local anesthesia. The first six post-partum days were uncomplicated. The blood pressure remained about 180/100. On the seventh day her temperature went to 101° F.; she complained of feeling faint, went into a short, generalized convulsion, and died suddenly.

Cerebrospinal fluid was clear. Blood urea nitrogen varied from 8.3 to 14, cholesterol 200, serum albumin 4.07, and serum globulin 2.57 mg. per cent. Urine showed a fixed specific gravity at 1.017, 2- to 4-plus albumin, hyaline, and granular casts.

At autopsy, significant findings were limited to the heart, kidneys, and brain. The heart weighed 525 Gm. and showed hypertrophy of both ventricles. No thrombi were found in any portion of the heart or pulmonary vessels. Coronaries were open in all of their main branches. Kidneys weighed 125 Gm. each, showed gross scarring of the cortical surfaces, and microscopic evidence of advanced arteriosclerosis. The liver showed no gross or microscopic evidence of hemorrhage.

The meninges and formalin fixed sections of the brain failed to show gross softening or hemorrhage. All microscopic sections showed medial and intimal hyperplasia of the arterioles and precapillaries. Congestion and small perivascular hemorrhages were present in the cerebellum and in the medulla beneath the floor of the fourth ventricle (Fig. 5). Death was attributed to advanced cerebral arteriosclerosis and multiple minute hemorrhages of the brain.
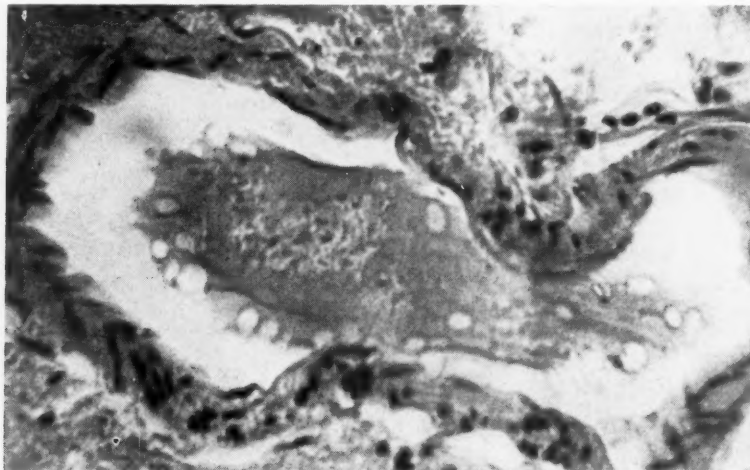

Fig. 5.--(Case 5.)   Photomicrograph showing rupture of an arteriole in the medulla (high power).

Fig. 6.—(Case 6.)   Eclampsia with convulsions and right hemiplegia.

Eclampsia With Convulsions and Hemiplegia

CASE 6.—L. G., white, primipara, aged 16 years, was admitted on Oct. 27, 1938, at term and in active labor. She had made one visit to a prenatal clinic on Sept. 12, 1938, where her blood pressure was recorded at 120/70. She had had scarlet fever at five years of age.

On admission the blood pressure was 200/140. Edema was generalized. Ophthalmoscopic examination revealed engorged veins, narrow, spastic arteries, and marked edema of the left disc and blurring of the right disc.

During the second stage of labor, the patient became extremely restless. With the aid of outlet forceps and ether anesthesia, she was delivered of a living infant weighing 6 pounds 5 ounces (2,863 Gm.). Her first eclamptic convulsion occurred at delivery. She had three additional convulsions at approximately one, two, and seven hours post partum. For forty-eight hours she remained semicomatose with a slow, irregular pulse, stertorous breathing, and a blood pressure which varied from 126/88 to 160/120. Sixty hours post partum the patient began to respond to questions, but was unable to speak. Her oropharynx was hyposensitive; tongue protruded to the right, and a flaccid paralysis of the right side of the body was present (Fig. 6). Spinal fluid was clear with no increase in pressure. When discharged from the hospital on the seventeenth post-partum day, she was able to walk alone. She had a right foot drop, a residual facial palsy, and some slurring of speech.

Blood urea nitrogen was 18, sodium chloride 576, serum albumin 2.38, serum globulin 2.19, calcium 13.3, and phosphorus 10 mg. per cent. Urine showed a specific gravity of 1.019, 4-plus albumin (Esbach 13 Gm. per liter), hyaline and granular casts.

The consulting neurologists were of the opinion that eclampsia had been complicated by either thrombosis of, or hemorrhage from, the left middle cerebral artery in the Sylvian fissure.

We have been informed that this patient gave birth to a full-term infant on Dec. 29, 1939, at which time her blood pressure was normal and her only residual evidence of paralysis was a slight right foot drop.

Six patients representing the various types of serious intracranial complications occurring in the toxemias of pregnancy have been presented. In all six patients the spinal fluid and blood Kahn reactions were negative. Gross cerebral hemorrhage was present in four patients who died of eclampsia. One patient with chronic vascular nephritis died of multiple minute hemorrhages secondary to cerebral arteriosclerosis. One patient with eclampsia complicated by hemiplegia recovered.

Discussion

During the past four years, there has been an alarming increase in the toxemias occurring in pregnant patients admitted to Gallinger Municipal Hospital. All of the reasons for this recent rise in toxemia are not known. It is of immediate concern that 12 out of 41 patients with eclampsia had not even registered at a prenatal clinic. Only one (Case 5) of the six patients with toxemia and cerebral complications had received adequate prenatal care.

Hypertensive cardiovascular renal disease, not peculiar to pregnancy, accounted for 37 per cent of the patients classified in this study. Coincidentally, this same group of patients contributed 37 per cent of the total maternal mortality in the toxemias of pregnancy. In addition, chronic hypertensive vascular disease preceded the development of toxemia and cerebral hemorrhage in three out of the four fatal cases of eclampsia reported above. From these data it is apparent that patients with hypertensive vascular renal disease are poor candidates for repeated pregnancies.

In the management of toxemias of pregnancy at Gallinger Municipal Hospital, a preliminary impression is made regarding the type of toxemia which the patient presents. *Treatment is directed at the predominating factors in the toxemia.* In pregnancy with hypertensive vascular disease, vasodilators and sedation are given. Care is taken not to overload the vascular system with hypertonic intravenous medication. In all toxemias there seems to be a definite contraindication to the use of pituitrin due to its vasopressor and antidiuretic effects. The second stage of labor is shortened by reasonable operative means, remembering that patients with toxemia withstand trauma very poorly. When possible, local is substituted for inhalation anesthesia.

In severe toxemias of pregnancy, attention should be focused on the manifestations reflected in the most vascular and vital of the body tissues, namely, the brain, liver, and kidneys. Cerebrovascular changes of arteriospasm and edema give rise to headaches, visual and auditory disturbances, convulsions, and paralysis. If these are recognized early and treated properly, intracranial hemorrhage may be prevented. Because of deep sedation, failure to perform a thorough neurological examination, transitory character of some paralyses, or in a few instances where massive intracerebral hemorrhage blocks all motor pathways, the physician may fail to recognize and localize important intracranial lesions. Thrombosis and rupture of cerebral vessels are evidence of late and serious changes in the toxemias of pregnancy. Although the prognosis is poor, early recognition and intelligent neurological treatment offer the pregnant patient with cerebral hemorrhage her only chance for recovery.

References

1. Abbott, W. D.: J. A. M. A. 117: 1439, 1941.
2. Barrett, C. W., and Harger, S. B.: AM. J. OBST. & GYNEC. 60: 463, 1909.
3. Binder, J.: AM. J. OBST. & GYNEC. 15: 849, 1928.
4. Bouffe de St. Blaise: Lesions anatomique que l'on trouve dans l'eclampsie puerperale, Paris Thèse, 1891.
5. Caffier, P.: Med. Klin. 23: 162, 1927.
6. Carver, N. C., and Fairbairn, J. S.: M. Press & Circ. 85: 116, 1908.
7. Cronson, R.: Am. Med. 3: 260, 1908.
8. Dieckmann, W.: The Toxemias of Pregnancy, St. Louis, 1941, The C. V. Mosby Co.
9. Hajkis, M.: Lancet 1: 628, 1937.

10. Henriet, P.:   Bull. Soc. d'obst. et de gynéc. **21:** 489, 1932.
11. v. Hoesslin, R.:   Arch. f. Psychiat. **38:** 730, 1904.
12. King, A. G.:   J. A. M. A. **100:** 15, 1933.
13. Klebs, E.:   Beitr. z. path. Anat. u. z. allg. Path. **3:** 1, 1888.
14. Kosmak, G. W.:   The Toxemias of Pregnancy, New York, 1926, D. Appleton-Century Company.
15. Levant and Portes, L.:   Gynéc. et obst. **7:** 332, 1923.
16. Liebers, M.:   Arch. f. Psychiat. **105:** 57, 1936.
17. Liebich, E.:   Zentralbl. f. Gynäk. **36:** 1234, 1912.
18. McMann, W.:   Virginia Med. Monthly **63:** 310, 1936.
19. Maygrier and Chevane: Bull. Soc. d'obst. de Paris **2:** 410, 1899.
20. Meyer-Wirz: Arch. f. Gynäk. **71:** 24, 1904.
21. Mondy, S. L.:   Glasgow M. J. **59:** 339, 1903.
22. Pfannenstiel: Zentralbl. f. Gynäk. **11:** 601, 1887.
23. Rheindorf, H.:   Zentralbl. f. Gynäk. **56:** 2413, 1932.
24. Rhemann, F.:   Gyogyazat **75:** 246, 1935.
25. Schauta, F.:   Arch. f. Gynäk. **18:** 263, 1881.
26. Schmid, H.:   Ztschr. f. Geburtsh. u. Gynäk. **69:** 143, 1911.
27. Schmorl, G.:   Arch. f. Gynäk. **65:** 519, 1902.
28. Schulze, V. E., and Schwab, E. H.:   Am. Heart J. **11:** 66, 1936.
29. Schwanen, H.:   Zentralbl. f. Gynäk. **58:** 1394, 1934.
30. Slemons, J.:   Johns Hopkins Hosp. Bull. **18:** 448, 1907.
31. Welch, J.:   Bull. Lying-in Hosp., N. Y. **3:** 37, 1906.

SCLEROSIS AND RELATED SENILE CHANGES OF THE FALLOPIAN TUBES

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IT WAS noted in the pathology laboratory of Harper Hospital that a large proportion of the cases with leiomyofibromas of the uterus also showed the sclerotic and other changes in the Fallopian tubes of middle and advanced age.   Investigation of this relationship brought out several important points of interest.

The tube alterations accompanying the sexual climacteric, and therefore presumably due to ovarian deficiency, have received little attention in gynecologic literature.   This is particularly true of this country.   In fact, a rather thorough search of the recent literature failed to reveal in the English language any complete description of the changes.   A partial exception to this statement is the article by Novak and Everett,[1] in which the epithelial changes are described, but the striking and earlier alterations of the apparently more sensitive connective tissue are largely passed over.   Textbooks on gynecology, and even those dealing specifically with pathology, make very brief or no mention at all of the subject.   In the foreign literature, however, there are a few good descriptions to be found.   Of these, perhaps the most accurate is in the article by Tietze.[2]   Consequently, the following brief description follows this paper closely, except for a few points not mentioned by Tietze, or

others with which the observations made in the present study do not agree.

Description of Senile Changes of the Fallopian Tubes

In many women nearing the menopause and in all after this time there develop certain changes in the Fallopian tubes. First of all, the connective tissue shows an increase in fibrillar elements, becomes relatively less cellular, and takes more and more the eosin stain. As a consequence of this connective tissue hypertrophy, the folds become broader and plumper and tend to lose their convolutions. The cyclically changing epithelium shows little or no alteration at this time. As sclerosis advances, the tube folds are largely obliterated until finally three to ten years after the menopause they appear as broad, fingerlike, stumpy elevations with only a few secondary folds. According to Tietze the elastic
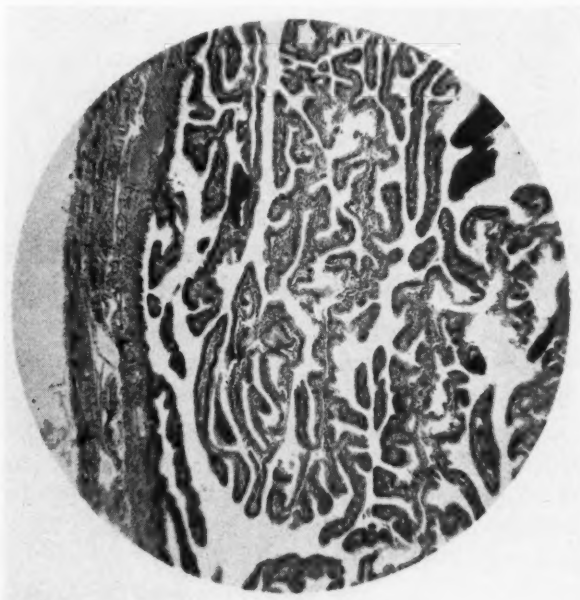
Figs. 1, 2, and 3 are of the same magnification, and are all from the same portion of the outer third of the tube.
Fig. 1.—Normal Fallopian tube.

fibers entirely disappear except for a few to be found in the tube wall. With these more advanced changes in the connective tissue the epithelium has a loss of ciliated cells and a relative increase of nonciliated or secretory cells. Meanwhile, here and there in widening areas or patches there is a progressive diminution in height of the cells, resulting in an irregular level. Finally, six to ten years after the menopause the cells have become cuboidal, or almost flat in places, and without cilia so that there is eventually a resemblance to prepubertal epithelium.

Tietze pointed out that the effect of the connective tissue changes is more striking toward the distal end of the tube where folds are normally more numerous, slender, and long. This observation was confirmed by the examination of sections from various parts of a number of tubes.

However, in every instance where a definite, even though slight, degree of sclerosis was present in any one section, it could be demonstrated elsewhere in the tube. The reverse also seemed true; that is, where one section is normal, the other parts of the tube likewise will fail to show
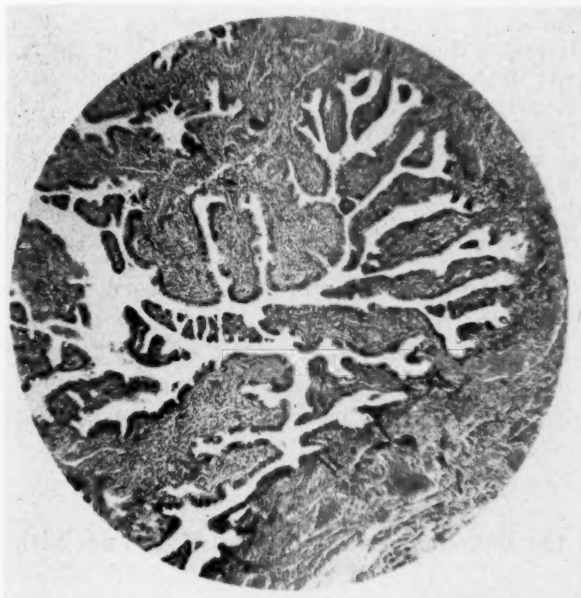

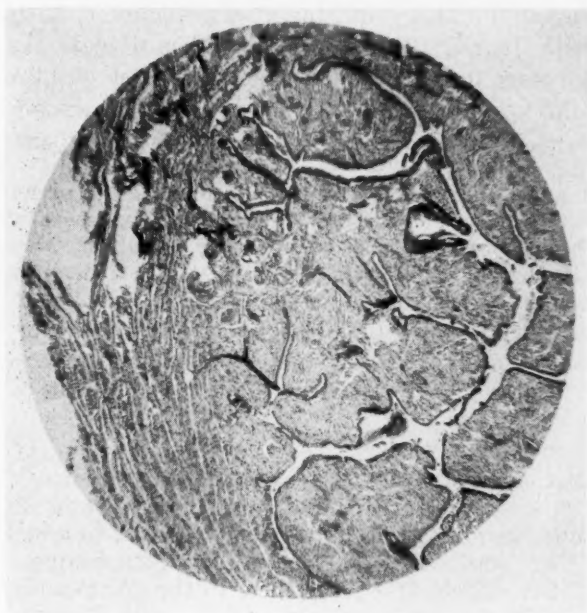Fig. 2.—Moderate sclerosis of the Fallopian tube.

Fig. 3.—Advanced sclerosis of the Fallopian tube.

definite sclerosis. It is also noteworthy that occasionally there was some difference in degree of sclerosis for the two tubes from the same patient, but in no instance was it entirely lacking in a tube when definitely present on the other side. Novak and Everett state that the epithelial changes also show a variability in different parts of the tube. A point of minor interest is the fact that crowding together of the folds in advanced sclerosis is due not only to hypertrophy of the connective tissue but in part to the well-known shrinkage and diminution in the size of the tubes occurring in women nearing, at, and past the sexual climacteric. The accompanying microphotographs (Figs. 1, 2, and 3), which are the same magnification and from the same part of the distal third of the tubes, illustrate the marked alterations in the folds due to sclerosis and also indicate by the difference in the arc of the tube walls the shrinkage and lessening in caliber of tubes after the menopause.

It is noted that the above description is in accord with the intimation given before that the connective tissue changes are not only evidenced earlier than are those of the epithelium but are also more striking. Consequently, the tube changes can be referred to subsequently by the brief term of ''sclerosis.'' The failure in the various parts of this paper to differentiate statistically between the grades or degrees of sclerosis is explained, of course, by the small numbers involved.

Sclerosis of the Fallopian Tubes in Cases With and Without Fibroids of the Uterus

As noted before, attention to this subject was attracted by the seeming high proportion of fibroid uteri with accompanying sclerosis of the tubes. To investigate this point, the hysterectomies at Harper Hospital beginning with Jan. 1, 1941, were reviewed until near the end of six months there were available 100 consecutive cases (approximately 46 per cent of the total number of 219 abdominal hysterectomies done during this time) selected to conform to the criteria given below.

1. One or more definite fibroids in the uterus 2 cm. or more in diameter. (This point was determined not only by the operative and gross pathology descriptions but also by a review of all the microscopic sections. In this way questionable cases and those with quite small leiomyofibromas were eliminated from the series.)

2. At least one Fallopian tube removed and available for study.

3. At least one ovary removed and available for study.

4. No old or recent salpingitis of a degree sufficient to distort the pathologic picture.

5. No evidence of pregnancy.

6. No radiation treatment more than six weeks previously.

Of these 100 cases the surprising number of 45 showed sclerosis of the Fallopian tubes varying from a slight, but definite, to a marked degree. In 7 others there was considerably more than a suggestion of the condition but still not sufficient to place them in the group with unquestionable changes. This high incidence of sclerosis with fibroids immediately introduced certain lines of speculation. For instance, since the changes are presumably due to ovarian deficiency, then here should be a potent

argument against a theoretical estrogenic excess as the cause of uterine leiomyofibromas. Again, the tube changes, or perhaps their cause, would offer some explanation for the higher incidence of infertility with fibroids and likewise the frequent futility of any and all treatment in these cases.

These and other conjectures offered reason for further investigation of the apparent high incidence of the tube changes associated with leiomyofibromas of the uterus. Considering the possibility that the size and mass of the tumors might have some influence on the tubes by pressure, by altering the circulation, or in some other way, the 100 cases were divided into groups graded according to the size of the uteri as compared to various periods in pregnancy. Although this is obviously a rough method of comparison, it should be sufficiently accurate to show any marked tendency even in this small series. Actually, as indicated in Table I, the incidence may possibly be some higher with the large tumors, but the differences are too slight to have any real meaning.

TABLE I. SIZE OF FIBROIDS AND SCLEROSIS OF TUBES

UTERI OF SIZE CORRESPONDING TO PREGNANCY	WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTAL
Up to 11 weeks	17	23	40
12 to 19 weeks	10	16	26
20 up to 23 weeks	7	8	15
24 weeks and over	11	8	19
	45	55	100

The investigation of age in relationship to sclerosis of the tubes was more successful (Table II). In fact, the differences were so striking as to suggest age, and not the presence of fibroids, as the likely factor of importance. To test out this idea, a comparison was made with a similar number of hysterectomy cases which fell into the same age groups as

TABLE II. WITH FIBROIDS. INCIDENCE OF SCLEROSIS OF FALLOPIAN TUBES ACCORDING TO AGES OF THE WOMEN

AGES	WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTAL
25-29	0	2	2
30-34	0	6	6
35-39	2	16	18
40-44	12	12	24
45-49	14	13	27
50-54	12	6	18
55 plus	5	0	5
	45	55	100

TABLE III. WITHOUT FIBROIDS. INCIDENCE OF SCLEROSIS OF FALLOPIAN TUBES ACCORDING TO AGES OF THE WOMEN

AGES	WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTAL
25-29	0	2	2
30-34	1	5	6
35-39	5	13	18
40-44	8	16	24
45-49	13	14	27
50-54	11	7	18
55 plus	5	0	5
	43	57	100

the fibroid cases and which, except for the carefully determined absence of leiomyofibromas of even the smallest size, corresponded to the same criteria employed in the selection of the first series. The close correspondence of Table III with Table II leaves little doubt that the high incidence of sclerosis of the tubes which at first seemed connected with the presence of fibroids was actually related in great part to the ages of the women. (Certain interesting incidental data brought out in assembling this second series are treated in another section of the paper.)

Relation of Previous Pregnancies to Sclerosis of the Fallopian Tubes

Although the data in the preceding section indicated that advancing age, with its endocrine derangements, was the principal factor in the senile changes of the Fallopian tubes, it seemed possible that other hormonal alterations might be found to play a part. For example, it was thought that the history regarding past pregnancies might give some information for or against an endocrine imbalance as a cause of tube sclerosis. All but 15 of the patients with fibroids, and of the 100 without these tumors all but 16, had a clear history relative to pregnancies. It was no surprise that fewer women of the first series (i.e., with fibroids) were known to have had pregnancies than was the case in the second. The difference, though, was not so great as often stated, being 55 as opposed to 66. Table IV shows rather remarkably similar occurrences of sclerosis of the tubes in women with and without previous pregnancies. Furthermore, essentially the same correspondence also holds when the cases are further split up into groups with and without fibroids of the uterus.

TABLE IV. INCIDENCE OF SCLEROSIS OF THE FALLOPIAN TUBES IN RESPECT TO A HISTORY OF PREVIOUS PREGNANCY, AND ALSO WITH AND WITHOUT FIBROIDS OF THE UTERUS. ONE SERIES OF 100 CASES WITH AND ANOTHER OF 100 WITHOUT FIBROIDS OF THE UTERUS

		WITH SCLEROSIS	WITHOUT SCLEROSIS	TOTALS
Previous pregnancy	With fibroids	24	31	55
	Without fibroids	28	38	66
		52	69	121
No pregnancy	With fibroids	11	19	30
	Without fibroids	8	10	18
		19	29	48
Pregnancy uncertain	With fibroids	10	5	15
	Without fibroids	7	9	16
		17	14	31

It was thought that a determination of the lapse of time since the last pregnancy might perhaps give some lead as to the state of the endocrine gland balance with and without sclerosis. Unfortunately, in the relatively few instances among the two series of 100 each (with and without fibroids) which had an accurate history in this respect the last pregnancies in all but 2 cases had occurred five years or more before operation. This was considered too remote to convey any useful idea of the endocrine relationship to sclerosis of the tube.

Sclerosis of the Fallopian Tubes and Menstruation

The relationship of sclerosis of the Fallopian tubes to the menstrual history is shown in Table V. The two series of 100 each (with and

without fibroids of the uterus) were tabulated together since the numbers involved were small. It should be noted, however, that further justification for this was found in separate tabulations of the two series which were actually made but failed to show any significant differences between the two.

TABLE V. RELATIONSHIP OF SCLEROTIC CHANGES OF THE FALLOPIAN TUBES TO THE TYPE OF MENSTRUATION IN 200 PATIENTS (100 WITH AND 100 WITHOUT FIBROIDS OF THE UTERUS)

MENSTRUAL PERIODS	SCLEROSIS OF TUBES	NO SCLEROSIS
No change	15	48
Less (scantier or infrequent)	5	4
More (profuse or frequent)	44	55
None for 2 to 6 months	1	1
None for over 6 months	12	1
Bleeding after menopause	9	0
Menstruation not noted	2	3
	88	112

The data in Table V emphasize the general association of tubal sclerosis with sex hormone diminution and failure as evidenced by menstrual alterations and cessation. Where no menstrual changes were noted, there were relatively few instances of sclerosis of the tubes. Whereas, with disturbances in frequency or amount of the periods, about one-half of the patients had definite sclerosis of the tubes. And, after climacteric cessation of menstruation, the great majority of tubes were affected. Attention is particularly directed, however, to the exceptions in the general trend. These clearly indicate that sclerosis of the tubes has only a general correspondence to the menstrual history, sometimes preceding the menopause, but also in a few instances not yet appearing well after the climacteric.

Sclerosis of Fallopian Tubes and Histology of Ovary and Endometrium

A comparison of the occurrence of tubal sclerosis (in the two series of 100 each) with the presumable sex hormone status as indicated by the histology found in the ovary and endometrium is shown in Table VI. The presence, either alone or in combination, of a corpus luteum, a normal number of primordial and maturing follicles, or a definitely cyclical endometrium (late proliferative or secretory phases) was considered sufficient evidence to place a case in the normal gonadal division. Another group was made up of those with only an occasional follicle, which is sometimes the finding just before, at the time of, and for a few years after cessation of menstruation. And then came those with entire absence of follicles, or in other words senile ovaries. Since only one or two sections to each ovary were as a rule available for study, it is possible that a few of the cases in the last two groups, if more careful examinations were possible, actually should belong in the hormonally more active division. The most probable error in this table, then, would be in the direction of underestimating the number of more gonadally normal cases. Indeed, it might possibly be more correct to incorporate the second groups in the first ones. Actually, however, the numbers are small and so nearly equal that such a change would have no effect on the significance of the table.

The conclusions to be drawn from Table VI are essentially the same as those from Table V. With histologic evidences of diminution in female

TABLE VI. RELATIONSHIP OF SCLEROSIS OF FALLOPIAN TUBES TO FEMALE SEX HOR-
MONE ACTIVITY AS EVIDENCED BY HISTOLOGY OF OVARIES AND ENDOMETRIUM IN 200
CASES (100 WITH AND 100 WITHOUT FIBROIDS OF THE UTERUS)

	SCLEROSIS OF TUBES	NORMAL TUBES	TOTALS
Normal histology (corpus luteum, abundant follicles, cyclical endometrium)	43 (32%)	91 (68%)	134
Few primordial follicles	14 (54%)	12 (46%)	26
Senile ovaries	31 (78%)	9 (22%)	40
	88	112 (100%)	200

sex hormone activity, there is generally an increased incidence of senile
changes in the Fallopian tubes. Also, a similar finding is the fairly large
number of exceptions to the general tendency. Sclerosis of the tubes
may, and often does, occur before there are histologic evidences of female
sex gland failure. And, on the other hand, definitely senile appearing
ovaries do not always have associated sclerosis of the tubes.

A combination of the data in Tables V and VI was calculated and
might be of interest but was too complicated to be easily demonstrated
in tabular form. However, the tendency was as could be expected; i.e.,
histologic evidences of normal hormone activity and associated normal
tubes being usual with unchanged menstruation, less with anomalies of
the periods, and rarely found after the menopause. Again, though, ex-
ceptions to the rule were present in practically all categories.

Sclerosis of the Fallopian Tubes and Sterility

Since sclerosis of the tubes develops with advanced sexual age and is
presumably due to the ovarian hormone reduction or other endocrine
alterations of that period of life, sterility should be a likely accompani-
ment of the condition. Moreover, the enlargement and crowding together
of the tubal folds and also the loss of ciliated epithelium might well
interfere mechanically with downward transportation of ova. In sup-
port of the expectation of barrenness in these cases, there was no in-
stance of sclerosis of the Fallopian tubes associated with pregnancy found
in the index files at Harper Hospital. As a check on this, an attempt was
made to assemble 100 pregnancy cases with tubes available for study,
which would fall into the same age groups as the two series of cases
previously described. A review of the hundreds of operations for such
conditions as ectopic pregnancy, cesarean section with salpingectomy,
etc., during the last ten years quickly filled out the younger groups, but
the older ones were largely or totally deficient. However, a comparison
of this series (Table VII) with the other two (Tables II and III) indi-
cates that, in spite of the inadequacy of the older groups, at least a few
instances of sclerosis would have occurred in a similar series of non-
pregnant patients. Actually, an examination of the microscopic sections
showed that in the small series of pregnant women such was also the
case, there being found one instance of rather slight but definite sclerosis
and another with the condition moderately well advanced (Fig. 4). In
both instances the pregnancy was in the tube.

Because of the incompleteness of this series, no accurate statistical
conclusions can be drawn. Obviously, though, the fact that pregnancy
was discovered at all is sufficient evidence that neither the condition
itself nor its cause is an absolute barrier to fertilization of the ovum.

The question concerning the importance of either or both as a *relative* hindrance to pregnancy remains unanswered by this study. The same is true of the possible role of sclerosis as a cause of tubal pregnancy by mechanical obstruction to migration of the fertilized ovum through the Fallopian tube to the normal site of implantation in the uterus.
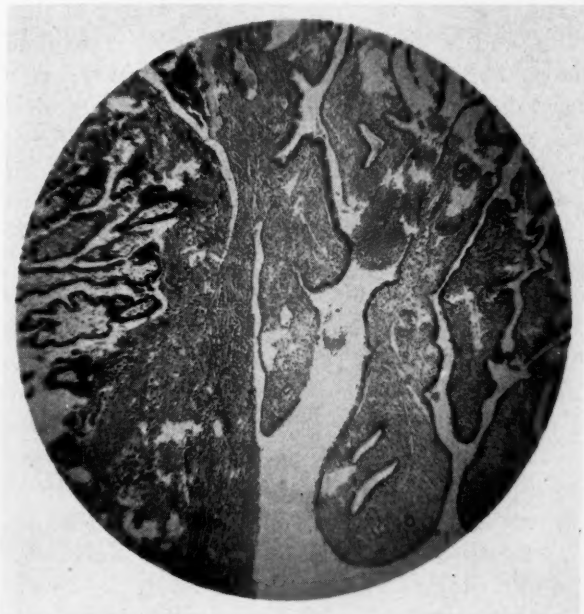
Fig. 4.—Moderately advanced sclerosis of the Fallopian tube associated with tubal pregnancy. The greatly enlarged and stumpy folds in the tube lumen on one side are separated by a partition from chorionic villi on the other.

TABLE VII. OCCURRENCE OF SCLEROSIS OF THE FALLOPIAN TUBES WITH PREGNANCY. (CASES INTENDED TO BE COMPARABLE IN AGES TO THE SERIES IN TABLES II AND III, BUT A REVIEW OF THE OPERATIONS FOR 10 YEARS FAILED TO FILL OUT THE OLDER GROUPS)

AGES	NO SCLEROSIS	WITH SCLEROSIS	TOTAL
25-29	2	0	2
30-34	6	0	6
35-39	17	1	18
40-44	12	1	13
45-49	–	–	0
50-54	–	–	0
55 plus	–	–	0
	37	2	39

Incidental But Important Points Suggested by the High Frequency of Leiomyofibromas in This Study

Not pertaining to the principal purpose of this study, but nevertheless of interest, were certain impressions derived from the indication of a generally high frequency of fibroids in the uteri removed at Harper Hospital. As previously stated, the first series of 100, or those with

fibromyomas, amounted to approximately 46 per cent of all the hysterectomies during a period of not quite six months. This percentage in itself, and without regard for additional fibroid cases not counted because of absence of tubes or ovaries, small size of fibromas, etc., is actually in excess of that reportedly found with and frequently believed to be significant in certain conditions, such as cancer of the body of the uterus, sterility, and pelvic inflammatory disease. Less definite, though perhaps equally impressive, were results obtained in the extensive search which was necessary for the collection of the 100 cases without fibroids. The 50 required for the age groups through forty-four years were secured from approximately 800 hysterectomies done during the year 1941 and most of 1940. For the older groups, however, it was necessary to go back, in addition, through 1939 and well into 1938 to find 50 suitable cases definitely without fibroids. This does not mean that all the remaining cases had fibroids. In fact, the majority were ruled out at the start on account of unsuitable age and without consideration of the presence or absence of uterine tumors; and others because of advanced pelvic inflammatory disease, pregnancy, or some other failure to conform to the criteria given before. In the cases remaining for study, however, a review of the operative records, the gross descriptions, and the microscopic sections showed considerably more than one-half with fibroids of appreciable size. Since in this part of the study an effort was made to select so far as possible cases with absolutely no leiomyofibromas, the remaining rejections were made in considerable part because of very tiny tumors. Obviously, in this last group the fibroids could not be considered "clinically significant," regardless of what may be meant by that very indefinite and variable and yet frequently used term. There is certainly the indication in these cases, however, that statistics involving fibroids of the uterus are likely to be meaningless unless the cases are selected in accord with definite standards regarding size of the tumors and other features, and unless comparison is made with control series.

In the literature there are also studies connecting fibroids and malignancy from the reverse point of view. For example, statements may be found to the effect that patients with fibromyomas of the uterus have a higher incidence of carcinoma of the uterine fundus than is the case in those without fibroids. This, if true, might be simply a reflection of the probable fact (at least so far as Harper Hospital is concerned) that on the average hysterectomy for fibroids is done later in life than for pelvic inflammatory disease and some other common indications. As a matter of fact, though, in the cases from Harper Hospital there was no instance of carcinoma involving the uterine body in the 100 fibroid uteri; whereas, in the other 100 without even small fibroids but which did correspond in age and other respects, there were 8 cases of fundus cancer. Results from these groups are admittedly far from trustworthy (because of small numbers and for other obvious reasons),

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but there is at least a strong suggestion here that properly comparable series might well revise the widespread impression that fibroids, or their etiologic factors, have a causal relationship to carcinoma of the uterus.

Summary

With advancing sexual age, the Fallopian tubes undergo certain changes consisting, first of all and most typically, of a marked hypertrophy and sclerosis involving the connective tissue of the folds. Later, there is also a replacement of ciliated epithelium by nonciliated and flatter cells. This sclerosis was noted in a high proportion (45 per cent) of cases with uterine leiomyofibromas. But the occurrence had little or no relationship to the size of the tumors. Moreover, an investigation of a like number of cases, which corresponded in all particulars except for the absence of even tiny fibroids, showed the condition in approximately the same proportion, the incidence increasing in both series with advancing age. Sclerosis of the Fallopian tubes showed no relationship to the history regarding previous pregnancies. The incidence of the condition was increased with the development of irregularities and anomalies of menstruation, and this was most marked with the onset of the climacteric and afterwards. The same tendency was noted also with the histologic evidences of sex hormone diminution. However, both here and with the menstrual changes there were definite exceptions to the general rules. Examination of a small series of tubes associated with pregnancy showed that sclerosis is occasionally present, and therefore it (or its cause) is not an absolute barrier to pregnancy. Left unanswered, however, were such questions as its possible role as a *relative* factor in sterility and also as a cause of tubal pregnancy. An interesting point incidental to the main purpose of this study was the discovery of such a high frequency of leiomyofibromas of the uterus in the material from Harper Hospital as to cast doubt on statistical studies which apparently indicate a relationship between fibroids and certain other conditions, particularly carcinoma of the uterine fundus.

References

1. Novak, E., and Everett, H. S.: Am. J. Obst. & Gynec. 16: 499, 1928.
2. Tietze, K.: Arch. f. Gynäk. 148: 724, 1932.

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A PRINCIPLE OF PHYSICS AS APPLICABLE TO SHOULDER DELIVERY*

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THE methods proposed for the extraction of the shoulders, as gathered from the current textbooks on obstetrics, are nearly uniform and do not differ materially from those taught a century or more ago. It is a fair criticism to state that not enough emphasis is given therein to the problem of the impaction of shoulders in its relation to the prevention of fetal death or lasting injury. In fact, both in teaching and in practice, it would appear that disaster attributable only to difficulty in shoulder delivery is to be accepted as an unavoidable incident.

Very few of our mechanical problems in obstetrics require emergency treatment. For example, if we have a persistent occipitoposterior position or a transverse arrest of the head, we usually have hours of warning and ample time in which, if necessary, to call in more expert help. Difficulty in the delivery of shoulders, however, usually comes as a complete surprise. We have no warning, a real emergency exists, and the minutes we have in which to make a safe delivery usually pass much faster than expert help can arrive.

It would not only be confusing, but it is unnecessary at this time to discuss the various shoulder presentations which may follow the delivery of the head. Instead, a simple, easily taught, working principle or plan will be presented, which can be applied to all shoulder problems.

This maneuver is based on a well-known law of physics applicable to the screw. A screw is a continuous spiral inclined plane, which when engaged in suitable threads is used where we wish to create the greatest resistance to its release by a direct pull. It follows, then, that a direct pull is the most difficult way to release a screw.

It will be demonstrated that a large baby in passing through a relatively small birth canal adapts, or must be made to adapt, the attitude of a screw, and that there are three "threads" in the female pelvis which prevent this large screwlike object from being released by a direct pull.

To illustrate this principle a wooden manikin has been constructed with shoulders so large that they cannot be delivered by a direct pull, or any textbook method. If, however, we maneuver it into the attitude of a screw it is just as easily released or unscrewed as a well-fitted

screw cap is released from a bottle.   But who has not had difficulty at times in releasing a screw from a bottle?   The reason for this difficulty is always the same, a crossed thread.   Unless we are able to correct the crossed thread attitude, we cannot without damage release a screw cap from a bottle.   We cannot release safely the shoulders of a large baby with a "crossed thread" unless we are able to correct the crossed thread attitude.
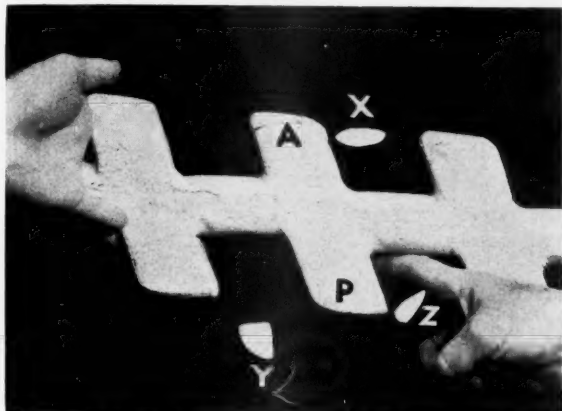
Fig. 1.—This figure shows a longitudinal section of a wooden screw engaged in three threads, X, Y, and Z.   Remembering the law of physics applicable to the screw we would waste no time in trying to disengage it by direct pull.   It is immediately apparent that the only way it can be released from its retaining threads is by turning in the proper direction.   Since it is a longitudinal section of a screw it has lost the advantage of the continuous spiral inclined plane, as a result of which it is necessary that the left hand produce a downward thrust synchronized with a lateral pressure with two fingers at P upward clockwise along the circumference of the arc to 12 o'clock.
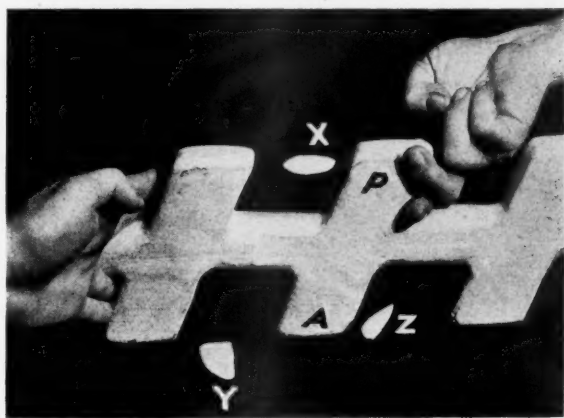
Fig. 2.—That part of the screw marked P has now been released from the threads X and Z.   The part marked A has passed from its position behind thread X and now occupies the same position previously occupied by P.   Repeating this procedure, A can be released in the same manner.   So far the demonstration has been in strict accordance with the law of physics applicable to the screw.   It cannot be released by a direct pull.   It can be released only by turning.

Incidentally, this same principle of physics is applicable to most of our mechanical difficulties in the delivery of the head of a baby. A persistent occipitoposterior position, and transverse arrest, are two examples of "crossed threads." Most maneuvers have been devised to prevent or correct a "crossed thread" attitude of some part of the baby's body. A series of pictures (Figs. 1 to 16) is presented graph-
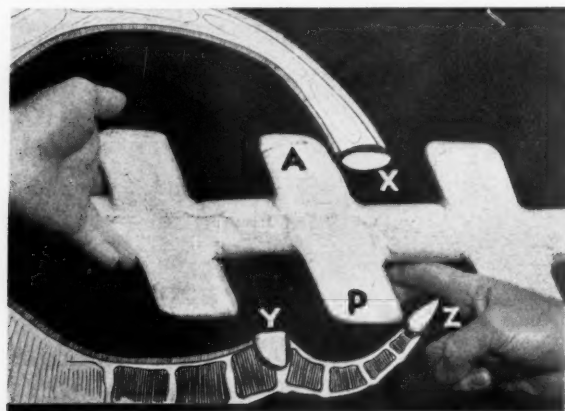
Fig. 3.
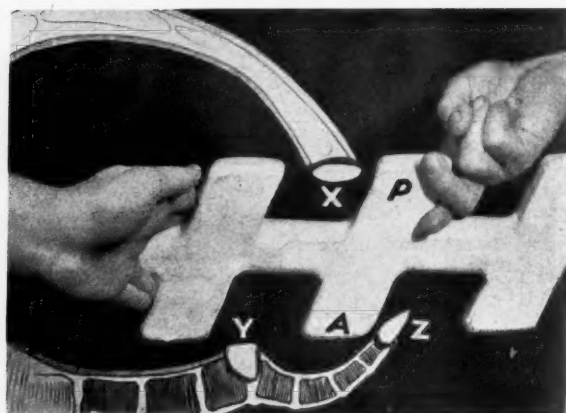
Fig. 4.

Figs. 3 and 4.—In these figures a longitudinal section of the maternal pelvis is superimposed upon these three threads, but does not in any way change or alter the mechanical principle involved. We still have three threads, X, Y, and Z, in exactly the same relative position, except that now we recognize them as the "pubic thread" X, the "promontory thread" Y, and the "coccyx thread" Z. The screwlike object cannot be released by pulling. It can be released only by turning.

ically to illustrate this maneuver. The legends beneath these pictures describe fully the principle and procedure, step by step.

Recapitulation of Technique

1. *In Vertex Presentation.*—A downward thrust is made with the left hand on the buttocks of the baby. At the same time two fingers of
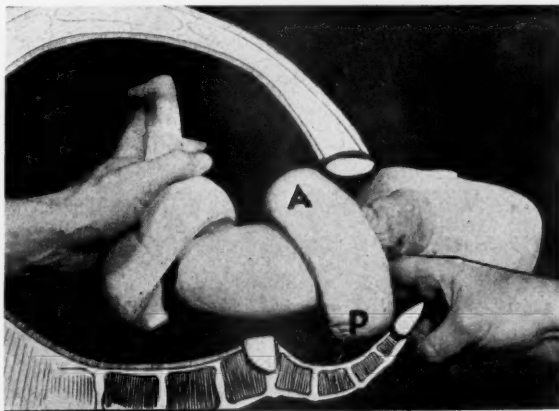
Fig. 5.
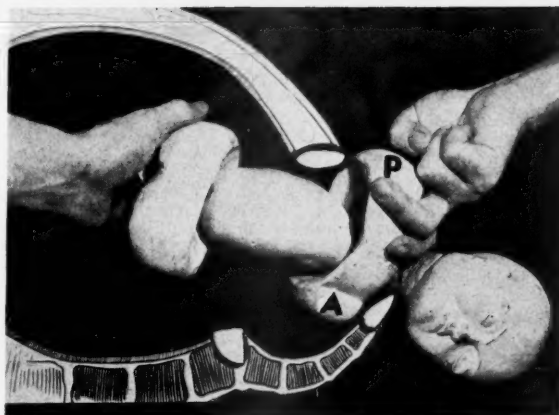
Fig. 6.

Figs. 5 and 6.—These figures show, engaged in these three threads, a wooden manikin with shoulders so large that they cannot be delivered by pulling. There is not enough room to force the hand under the "pubic thread" in an attempt to pull the anterior shoulder out. There is not enough room to force the hand into the crowded hollow of the sacrum. There is, however, ample room to insert two fingers between the baby's head and shoulder without touching the maternal parts except at the labia. A downward thrust is made with the left hand on the buttocks of the baby. At the same time two fingers of the right hand, on the anterior aspect of the posterior shoulder, make gentle clockwise pressure upward around the circumference of the arc to, and past, twelve o'clock. The posterior shoulder is now delivered.
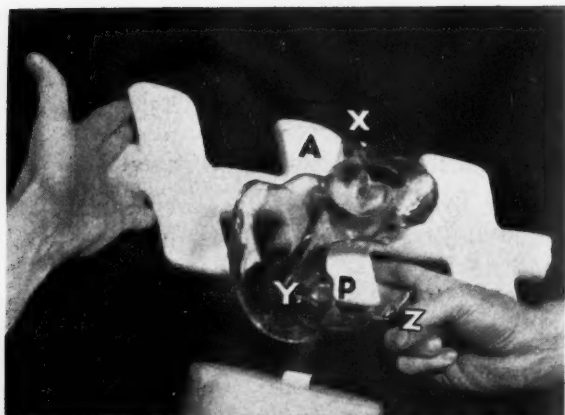
Fig. 7.

Fig. 8.

Figs. 7 and 8.—This is an exact reproduction of a normal gynecoid pelvis made from plastic glass, so that by suitable lighting the various models can be watched as they pass through the pelvis. The three threads, "pubic thread" *X*, "promontory thread" *Y*, and the "coccyx thread" *Z*, interfere with the release of the second part of the wooden screw which corresponds to the shoulders. It cannot be released by *pulling*. If, however, precisely the same maneuver is used as that employed in releasing the wooden screw in Figs. 3 and 4, this rigid wooden screwlike object can easily be released from the actual pelvis.

Fig. 9.—*(See opposite page for legend.)*

the right hand, on the anterior aspect of the posterior shoulder, make gentle clockwise pressure upward around the circumference of the arc to, and past, twelve o'clock.   The posterior shoulder is now delivered.

With pressure applied downward from above with the left hand the two fingers of the right hand make gentle counter-clockwise pressure upward around the circumference of the arc to and past twelve o'clock,

Fig. 10.

Figs. 9 and 10.—Fig. 9 shows what happens as a result of this pressure.   The anterior shoulder is impeded in its downward progress by the "pubic thread."   The "pubic thread," acting as a fulcrum, causes the posterior shoulder to descend into the hollow of the sacrum until it has passed the spines.   As soon as the posterior shoulder has passed the spines, the two fingers of the right hand start making gentle clockwise pressure on the anterior aspect of the posterior shoulder upward around the circumference of the arc to and past twelve o'clock.

Fig. 10 illustrates the chief cause of failure when this maneuver is first attempted. Many operators try to turn the shoulders at this point.   It is impossible.   From a mechanical standpoint the shoulders are now in a position known as a crossed thread. It is just as impossible to turn shoulders with a "crossed thread" as it is to remove a screw cap from a bottle with a crossed thread.   The next step is to correct this "crossed thread" attitude.   The buttocks of the baby are firmly grasped with the left hand and slow gentle pressure is made toward the pelvis.

Fig. 11.—The posterior shoulder has now been delivered.

and the remaining shoulder is delivered.   Again the pressure was made away from the perineum.   Sometimes it takes a little practice to get the pressure of the two hands properly synchronized.   The turn cannot be made until the posterior shoulder has passed the spines.

Fig. 12.—The anterior shoulder has passed from its position behind the pubic bone through an arc of 180 degrees and now occupies precisely the same position previously occupied by the posterior shoulder.   In passing from its position behind the pubic bone to the hollow of the sacrum it has exerted no pressure on the perineum.   Two fingers are inserted between the baby's head and shoulder and are finally placed, as illustrated, on the anterior aspect of the remaining shoulder.   With pressure applied downward from above with the left hand, the two fingers of the right hand make gentle counterclockwise pressure upward around the circumference of the arc to and past twelve o'clock, and the remaining shoulder is delivered.

Fig. 13.—Again the pressure was made away from the perineum.   Sometimes it takes a little practice to get the pressure of the two hands properly synchronized. The turn cannot be made until the posterior shoulder has passed the spines.

2. *In Breech Presentation.*—The technique is identical with that for vertex presentation except that the expulsion force is applied by gentle traction on the legs instead of downward pressure on the buttock.

3. If the baby's back presents toward the right the turning is clockwise. If its back presents toward the left, the turning is counterclockwise.
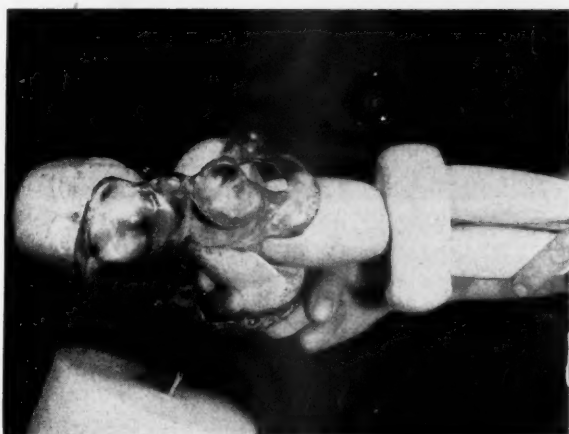
Fig. 14.
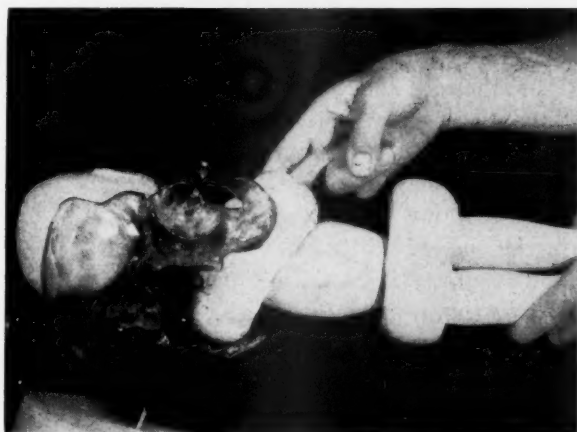
Fig. 15.

Figs. 14 and 15.—Illustrating how the same mechanical principle is applied to the shoulders in the breech delivery. Gentle traction is made by pulling on the feet with the left hand. The anterior shoulder becomes impeded in its downward progress by the pubic bone. The pubic bone, acting as a fulcrum, causes the posterior shoulder to swing down into the hollow of the sacrum. After the posterior shoulder has passed the spines (it is impossible before) two fingers of the right hand make gentle clockwise pressure on the anterior aspect of the posterior shoulder upward around the circumference of the arc to twelve o'clock, and the posterior shoulder is easily delivered. The arm is now brought downward with a wiping motion across the chest, and it, too, is easily delivered. The remaining shoulder is delivered by making gentle counterclockwise pressure with two fingers of the left hand on the anterior aspect of the shoulder upward around the circumference of the arc to twelve o'clock. The arm is then brought downward across the chest.
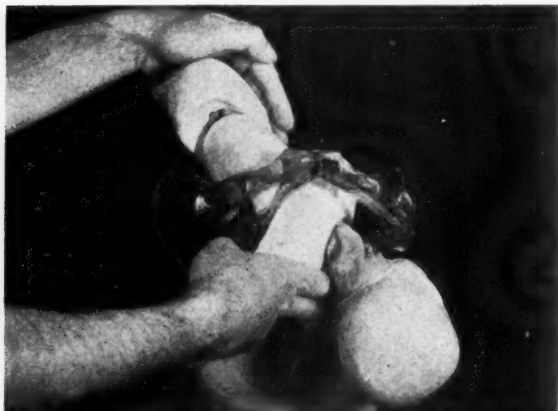
Fig. 16.—Illustrating the position of the operator at the side of the patient in performing this maneuver.

Summary

1. A wooden manikin, with shoulders too large to be delivered by pulling, is easily delivered according to a law of physics applicable to the screw.

2. If the shoulders of a wooden manikin are so large that they can be delivered in only one way, it would seem that this way would be the easiest, and therefore the least dangerous, way to deliver a live baby.

3. After the head has been born the shoulders of the baby resemble a longitudinal section of a screw engaged in three threads, the "pubic thread," the "promontory thread," and the "coccyx thread."

4. Any pulling on the baby's neck or axilla is mechanically incorrect because it violates a simple, well-known law of physics applicable to the screw.

5. There is no stretching of the trapezius muscle, and consequently no danger of injuring the cervical nerves.

6. The pressure is away from the perineum.

7. This maneuver cannot be performed unless the posterior shoulder has passed the spines.

8. Pressure from above, on the buttocks, must be applied by the operator (not an assistant) in order to synchronize the pressure of the two hands.

9. The passage of a baby through the birth canal is, in the vast majority of cases, an engineering problem. By applying a law of physics applicable to the screw, we find that most of our difficulty is due to a "crossed thread" or improper inclination of some part of our screwlike object. For example, extension of the arms, or nuchal arms, in a breech delivery may prevent the shoulders from adopting the proper inclination or screwlike attitude necessary for delivery. In the vertex presentation extension of the arms along the baby's body may interfere with the proper inclination of the shoulders. A Bandl's ring does the same thing.

THE EFFECT OF LOCAL ANESTHESIA BY MEANS OF PUDENDAL NERVE BLOCK WITH NOVOCAIN ON CERVICAL DYSTOCIA OCCURRING LATE IN THE FIRST STAGE OF LABOR*

A Preliminary Report

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H UNT and McGee[1] in a recent article state: "One of the most trying dilemmas encountered in obstetric practice is with the patient who, after many hours of active labor, presents urgent indications for delivery but presents an incomplete dilatation of the cervix. Cesarean section usually is not merited because there is no actual bony disproportion, or is contraindicated by frank or potential infection. Manual dilatation of the rigid cervix now is branded as 'manual tearing' and is condemned because of the dangers of trauma and hemorrhage, with morbidity both immediate and remote." With these remarks the majority of practicing obstetricians are in full agreement.

In their article, from which the above paragraph is quoted, they review their findings in the use of Dührssen's incisions in a series of 592 cases and conclude that it offers a rapid surgical method to complete dilatation of the cervix when urgent need for delivery arises, and when the almost fully dilated but resistant cervix is the only obstructing factor. The procedure which they used was first described by Dührssen in 1896. Williams[2] has remarked concerning this operation: "Unfortunately, it requires some surgical skill on the part of the operator, as well as specially devised specula, and the aid of several competent assistants, so that its use must be limited to trained specialists."

Although Dührssen's incisions constitute a clean surgical procedure, and would be expected to limit the injuries which accompany manual dilatation, it would be more desirable to paralyze the partially dilated spastic cervix by means of the nerve block technique with a local anesthetic such as novocain. If this aim could easily and readily be accomplished, the cervix would become fully dilated, or become so non-resistant that further dilatation could be accomplished by repeated small doses of pituitary extract or by manual means without any danger of

appreciable trauma. The purpose of this paper is to present such a procedure, which has been used over a considerable period of time with reasonably good results.

A number of articles have appeared in the recent literature on the use of novocain as a local anesthetic in obstetric practice. The various methods of administration involved the sacral, epidural, parasacral or presacral approach. Some of the investigators reporting on this type of anesthesia employed it in routine deliveries, while others emphasized its value in various complications other than cervical dystocia.

Bickerstaff[3] used sacral block anesthesia by means of low sacral injection of 2 or 3 per cent procaine in 55 routine deliveries, and in 10 cases where it was used solely for operative delivery or as expectant treatment of dystocia, preliminary to operative intervention. However, in addition to the many advantages of this method which he cites, he admits that obesity or sacral edema may render his procedure technically inapplicable. He adds: "It is difficult, even with considerable practice, to enter the sacral canal with the patient lying on her side, particularly with stout, flabby, overlying tissues, often edematous, sagging as much as an inch or more, and distorting the surface anatomy." Local skin lesions are, of course, another contraindication, as pointed out by the same author.

An easier method is that of pudendal nerve block by the presacral approach. But, as Waldman[4] points out: "Since 1910 a number of papers have appeared in the literature advocating pudendal anesthesia, but standard textbooks make no mention of this method, and the literature concerning it is surprisingly scarce in comparison to the voluminous reports on other methods of analgesia and anesthesia." Waldman does not present any clinical material, but merely discusses the advantages, indications and technique of pudendal nerve block. Urnes and Timerman[5] advocate its use routinely in spontaneous breech deliveries. Abrams[6] used pudendal nerve block in 400 routine deliveries. Some of the advantages of this method stressed by these authors are: (1) It may be used in home practice, when there is a lack of trained assistants to administer inhalation anesthesia and to control the patient when she is unconscious. (2) The patient is awake at all times and is able to cooperate in such procedures as repair of episiotomies. (3) The pelvic floor is relaxed to such a degre that an episiotomy is often not necessary and if so can be performed without additional anesthesia. (4) Eclamptic and preeclamptic patients are especially susceptible to pneumonia, and inhalation anesthesia is contraindicated in such cases. (5) There is no maternal or fetal mortality resulting from this method. (6) The uterine musculature is not involved, so that there is no interruption of uterine contractions during the second stage. This factor also lessens the likelihood of the need for manual removal of the placenta or the occurrence of post-partum hemorrhage. (7) Breech deliveries are facilitated because of the ability to obtain marked relaxation of the pelvic floor, without relaxation of the uterus.

While these advantages are obvious, it is proposed to confine the present paper to the use of pudendal nerve block as the method of choice in cervical dystocia, and discuss some of the theoretical aspects of its

mode of action.   Those types of cervical dystocia which result from cephalopelvic disproportion, radium therapy, laceration from previous deliveries, or other conditions which interfere with the normal anatomy of the cervix are to be eliminated from this consideration.

No attempt will be made to give a complete description of the nerve supply to the uterus, because there still exists much controversy on this subject (Fig. 1).
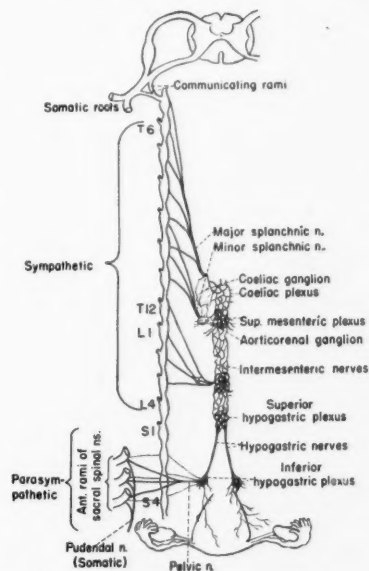
Fig. 1.—Anatomic distribution of the somatic and autonomic nerve fibers of the pelvic viscera.   (Modified from Mussey and Wilson, AM. J. OBST. & GYNEC. 42: 760, 1941.)

It is a well-known fact that the sympathetic nervous system supplies most of the nerves to the pelvic organs, and only a few fibers are derived from the parasympathetic system.   Recently Labate[7] published the results of a study on the anatomy of the superior hypogastric plexus, based on 75 dissections.   We quote from his article:

"*Motor Component of the Superior Hypogastric Plexus.*—Two or more parallel nerve bundles are arranged over the anterolateral surface of the aorta, usually one, or perhaps two, on each side.   These are known as the intermesenteric nerves.   They originate from the inferior pole of the coeliac plexus, at the level of the superior mesenteric artery, and descend over the anterolateral surface of the aorta.   Below the point of bifurcation of the abdominal aorta into right and left common iliac arteries the intermesenteric nerves become the main components of a triangular shaped plexus—the so-called superior hypogastric plexus. This plexus descends for a distance of 6 to 8 cm., overlying the lumbar vertebrae in the space between the right and left common iliac arteries. Over the middle of the first sacral vertebra the superior hypogastric plexus divides into the right and left inferior hypogastric nerves.   Each of these continues downward to the lateral rectal space, where it ends

in the inferior hypogastric plexus. From the latter fibers are distributed peripherally to the pelvic viscera. The afferent or sensory fibers probably pursue a course similar to the efferent or motor nerves. . . . The intermesenteric nerves, before descending over the aorta, also receive peripheral rami from the lumbar sympathetic ganglia.''

The pudendal nerve is derived from the second, third, and fourth sacral nerves. It leaves the true pelvis through the greater sciatic foramen and then curves over the spine of the ischium, beneath the gluteal muscles. It enters the anal portion of the perineum through the lesser sciatic foramen, and runs along the lateral fascial wall of the ischiorectal fossa, in the space known as Alcock's canal. The latter is
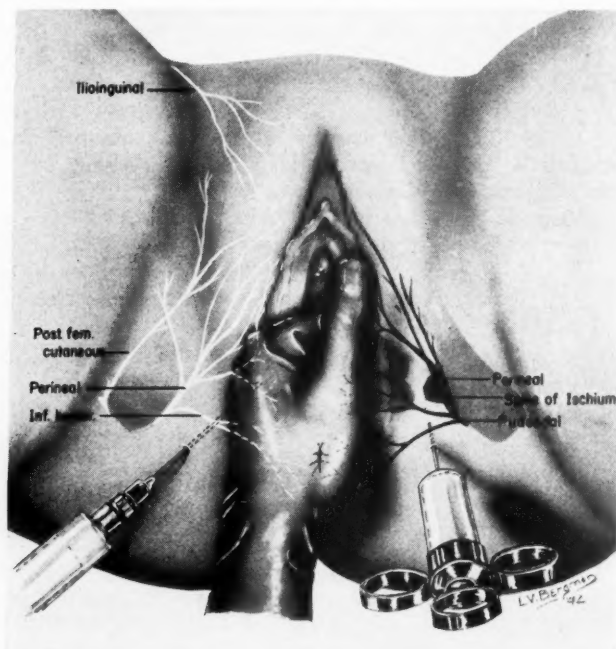
Fig. 2.—Diagram showing the procedure used for blocking the nerve supply to the pelvic floor.

anatomically and surgically important, for it is here that the pudendal nerve is blocked, as will be described further on. In Alcock's canal the pudendal nerve is accompanied by the internal pudic vessels and all together run forward in a groove on the inner border of the tuberosity of the ischium, immediately in front of the attachment of the sacrotuberous ligament.

Other parasympathetic fibers arise from S1, S2. and sometimes from S3 or from S2, S3, and S4 and unite to form the pelvic nerve, which terminates in the inferior hypogastric plexus.

Procedure

With the patient in the lithotomy position, the ordinary technique of preparation is carried out. One-half ounce of Scott's solution may be instilled into the vagina, if an antiseptic solution has not been used

previously. The index and middle fingers of one hand are inserted in the vagina and the ischial spine is located and used as an anatomic landmark. A No. 19 needle attached to a 20 c.c. syringe is inserted medially, half way between the rectum and tuberosity of the ischium. When the needle is felt by the vaginal fingers it is directed downward and laterally to a point just below the ischial spine. This directs the needle into Alcock's canal. Then 20 c.c. of 1 per cent novocain is injected at this point. One must always remember to pull back the plunger before injecting the solution, for, as pointed out above, the pudendal nerve is accompanied by the internal pudic vessels in its course through Alcock's canal. The needle is left in situ and the syringe is disconnected, refilled with 15 c.c. of the solution of 1 per cent novocain, and reattached to the needle. The latter is withdrawn slightly and directed against the ischial tuberosity, where the anesthetic is injected around the lateral cutaneous femoral nerve. Then 15 c.c. of 1 per cent novocain is injected superficially in an oblique and radial manner from the original site of insertion of the needle, to the inner aspect of the labium majus, thus paralyzing the terminal branches of the ilioinguinal nerve. A similar procedure is carried out on the opposite side. Thus, a total of 100 c.c. of novocain is used for both sides. As seen from the above, the needle has to be inserted only in two places, one on the right and one on the left side, without the need for removing it entirely during each procedure (Fig. 2).

Indications

A. Maternal.—1. In severe exhaustion in spite of treatment, when progress has been arrested in the course of a prolonged labor apparently due to the resistance of a rigid rim of cervix.

2. In serious pre-eclampsia or eclampsia when rapid dilatation of a rigid cervical rim may become desirable.

3. In cardiac decompensation during labor, when the rapid elimination of a rigid cervical rim is of importance before delivery can be accomplished safely.

4. In any emergency, such as abruptio placentae with concealed or external bleeding, when labor is well advanced but a cervical rim still exists.

B. Fetal.—1. Prolapsed cord in the presence of a resistant cervical rim.

2. Marked or progressive irregularities of fetal heart sounds, or passage of meconium under the same circumstances.

Results in 38 Cases

Thirty-eight patients were treated for cervical dystocia late in the first stage of labor by the technique described above. Thirty-one of the patients were primiparas and 7 were multiparas. There were no maternal deaths among the 38 cases.

There was one stillbirth, due to intracranial injury following the application of forceps, in a case of cephalopelvic disproportion.

Generally about five to ten minutes after the anesthetic is injected, one notices a relaxation of the perineum. In another ten minutes the spasticity of the cervix disappears and dilatations progress satisfactorily if the uterine contractions continue. If there is uterine inertia, small repeated doses of pituitary extract (2 min.) will initiate further progress.

This procedure was satisfactory in the majority of our cases. In the case that failed, local anesthesia was likewise unsatisfactory. The explanation for this is that the pudendal nerve was probably not well anesthetized, or that the anesthetic solution was defective. It is essential that the novocain used be always freshly prepared. In neurotic individuals, we suggest a little gas anesthesia during the performance of pudendal block.

This procedure failed in one case. The patient, a para 0 at term, aged 43 years, with an unusually rigid perineum. The membranes had ruptured spontaneously twenty hours prior to admission. After being in the hospital for forty-eight hours, the patient began to have slight irregular contractions following medical induction. Labor continued for twenty-six and one-half hours when the cervix became four fingers dilated and remained at this stage of dilatation for six hours. Local block was tried, and after thirty minutes the cervix still remained spastic and the fetal heart became slightly irregular. Labor was terminated by Dührssen's incision and application of midforceps under general anesthesia. Mother and baby left the delivery room in good condition.

The average duration of labor for the 38 cases was 31.9 hours, and the average arrest of progress lasted 6.3 hours.

In one case there was no arrested progress, but the patient, para i, gravida ii, was admitted to the hospital with membranes ruptured and history of profuse hemorrhage two hours prior to admission. Bleeding had ceased when she came to the hospital because the head had descended and compressed the bleeding site. The fetal heart was slow. Labor pains were rather severe and on rectal examination the cervix was found to be thick and over three fingers dilated. The presenting part was a vertex and was at the level of the spines. Local block anesthesia was considered for two reasons: (1) to allow for rapid dilatation of the cervix without traumatizing it, and (2) to avoid using general anesthesia for fear of relaxing the uterus and causing recurrence of hemorrhage. Fetal distress necessitated rapid delivery. Within ten minutes after the local anesthesia, the cervix became completely dilated, and labor was terminated with low forceps, resulting in the delivery of a live baby in good condition.

In the majority of cases it was necessary to use pituitary extract in two or three minim doses because a state of moderate secondary inertia existed. Although some obstetricians would have tried pituitary extract without this method of block anesthesia, it has been observed by the authors that such use of oxytocics often fails to accomplish the desired results.

In this series, maternal exhaustion with a spastic resistant rim of cervix remaining at a standstill, for an average of 6.3 hours, was found to be the most frequent indication for intervention. Most cases required outlet forceps to complete delivery. Labor was terminated in every case after the use of local block anesthesia, and the average length of time from injection to the birth of the child was $21\frac{1}{2}$ minutes.

An episiotomy was done in every case and all healed by primary union with the exception of two. In these cases the sutures sloughed the third day, although the temperatures in both cases remained normal. The patients offered the ordinary complaints during the puerperium.

Two patients sustained cervical lacerations which were repaired after the expulsion of the placentas. These were examined on the day of discharge and found healed by primary union.

The average duration of ruptured membranes in the 38 cases was 11.9 hours.

Clinical Discussion

No attempt will be made to explain, from an anatomic or physiologic basis, the clinical results obtained in the type of cases in which this procedure was used. For, as pointed out above, there still exists much controversy as to the exact pathways of the nerve supply to the uterus. The hypothesis is advanced that reflex stimuli may be set up, as the result of local anesthesia of the pudendal nerve, which in some way affect uterine activity, particularly in relation to the cervix. The problem of the reflex activation of the uterus has been investigated on numerous occasions. As pointed out by Kuntz,[8] ". . . the data available at present speak against the existence of reflex connections in the autonomic ganglia (except in the peripheral plexuses), but physiological data is not wanting which strongly suggest that under certain conditions reflex reactions may be carried out through these ganglia. Sokownin (1874) observed that after all the nervous connections of the inferior mesenteric ganglia except the hypogastric nerves were out, stimulation of the central end of one hypogastric nerve elicited contraction of the bladder, the efferent impulses passing down the hypogastric nerve on the opposite side. Langley and Anderson (1894) confirmed this finding. They also observed that stimulation of the central end of one hypogastric nerve, under the same experimental conditions, also elicits slight pallor of the opposite cornu of the uterus, and rarely, slight contraction of this part of the uterus and the vagina.

"Stimulation of the mammary gland elicits uterine contractions which may give rise to painful sensations. Uterine contractions in response to stimulation of the breasts become more pronounced near the termination of pregnancy. Reflex reactions of the female genitalia also may be elicited by direct stimulation of any afferent nerve."

In view of the fact that favorable results have been attained with this procedure, even without an adequate neuroanatomic explanation of its mechanism, it is believed to be of sufficient interest and value to present to the medical profession for further consideration.

References

1. Hunt, A. B., and McGee, W. B.: AM. J. OBST. & GYNEC. 31: 598, 1936.
2. Williams' Obstetrics, Ed. 6, New York, 1935, D. Appleton-Century Co., p. 469.
3. Bickerstaff, H. J.: J. M. A. Georgia 35: 148, 1936.
4. Waldman, I. J.: Wisconsin M. J. 38: 552, 1939.
5. Urnes, M. P., and Timerman, H. J.: J. A. M. A. 109: 1616, 1937.
6. Abrams, S. F.: J. Missouri M. A. 35: 81, 1938.
7. Labate, J. S.: Surg., Gynec. & Obst. 67: 199, 1938.
8. Kuntz, A.: The Autonomic Nervous System, ed. 6, 1934, Lea and Febiger, pp. 80 and 350.

5605 TWELFTH AVENUE

THE ASSOCIATION OF VAGINAL BLEEDING TO ORGANIC PATHOLOGY AND THE ENDOMETRIAL PATTERN IN THE DECADES BEFORE THE MENOPAUSE

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THE commonest complaint of women presenting themselves to the physician is abnormal vaginal bleeding. In many instances the simplest examination seems to disclose the cause, in others careful diagnostic procedures are required, while in a considerable group the factors producing the bleeding are not known.

Material

A study of all patients in whom abnormal bleeding was a symptom, admitted to the Gynecological Service of Roosevelt Hospital from 1921 to 1935, provided the material for this presentation. During these years 12,350 patients were admitted to the wards. Abnormal bleeding in some form was noted in 4,362 patients, or 35.3 per cent, of whom 15.6 per cent gave no evidence of pregnancy. This may be compared with the report of Weintraub[1] who found that 16.6 per cent of 4,421 patients admitted to the gynecologic service of the Israel Zion Hospital (Brooklyn), presented with abnormal bleeding not due to pregnancy.

Of our entire series, 406 were classified as postmenopausal. They were over forty years of age and had experienced six months' amenorrhea before the bleeding occurred. These cases were analyzed in a previous paper by Taylor and Millen.[2]

The present study deals with 3,956 cases in women before the menopause. The age distribution is shown in Table I. This compares with the figures of Keene and Payne[3] who, in a series of 500 patients with functional bleeding, noted that 4 per cent occurred before twenty years; 21 per cent occurred between twenty and thirty; 25 per cent between thirty and forty; 41 per cent between forty and fifty; and 9 per cent between fifty and sixty years of age. Their inclusion of postmenopausal cases created a higher percentage in the last two decades.

The intent had been to study and reclassify all the microscopic slides of each case. Records from the earlier years frequently lacked the

TABLE I. AGE DISTRIBUTION OF CASES BEFORE MENOPAUSE

AGE BY DECADES	10-19	20-29	30-39	40-49	50	TOTAL
Cases with good endometrial slides available for restudy	10	216	181	409	69	885
Cases with no endometrial slides available	93	963	1,210	713	92	3,071
Total	103 (2.5%)	1,179 (29.8%)	1,391 (35.1%)	1,122 (28.3%)	161 (4.3%)	3,956

dates of the menstrual period before operation and endometrial section slides were often missing or inadequate to determine endometrial patterns. Hence the cases have been subdivided according to the value of the material for study as shown in Table I.

Classification of Causes of Bleeding

Classifications of the causes of abnormal vaginal bleeding usually make a basic subdivision between functional types without gross pathology on the one hand and organic lesions on the other. The latter include complications of pregnancy, malignant and benign tumors, inflammatory reactions and malpositions. There are also a few constitutional causes such as certain of the blood dyscrasias and perhaps vitamin deficiencies.

Complications of pregnancy are an important cause of abnormal vaginal bleeding, but this is a subject for special consideration elsewhere. It may be noted, however, that in this series out of 3,956 cases of vaginal bleeding in women before the menopause, 861, or 21.8 per cent, were due to miscarriage, ectopic pregnancy, or hydatidiform mole. Rongy[4] found 1,167 such complications among 2,175 patients admitted to the gynecologic service at the Lebanon Hospital, New York City.

Cancer as a cause of bleeding is only of statistical interest, for the mechanism of the hemorrhage is quite obvious. In this series, malignant tumors numbered 611, or 15.4 per cent. Ovarian cancer must be considered from a somewhat separate viewpoint because here the bleeding is likely to come from an endometrial reaction to hormones produced by the tumor tissue. Shaw,[5, 6] Meyer,[7] and, more recently, Seegar and Jones[8] have described such cases. A similar relationship between vaginal bleeding and benign ovarian tumors may also exist.

The *benign tumors* which may cause bleeding are chiefly fibromyomas, benign ovarian tumors, and polyps. Fibroids are, of course, the most important and the manner in which they cause bleeding is of interest. As pointed out by Burch,[9] the bleeding in fibromyoma is due in some instances to a functional disturbance manifested in a peculiarity of the endometrial pattern and not to the fibromyoma itself. Morse[10] claims that myomas produce menorrhagia until they undergo necrotic changes when metrorrhagia ensues. Jones[11] emphasizes that bleeding occurs when a fibroid projects into the cavity, and Burch[9] also believes that erosion of the tumor through interference with the blood supply may lead to bleeding. The excess endometrium overlying a fibroid has also been suggested as a cause of the bleeding (Faber[12]).

The relationship of the ovarian hormones to fibroids has received considerable attention. Witherspoon[13] believes that fibroids and hyperplasia of the endometrium associated with follicular cysts are the result of the hormonal activity of the cysts. As reported by Twombly and Millen,[14] pellets of estrogenic hormone inserted to produce a prolonged therapeutic effect in the menopause are capable of rapidly increasing the size of existing fibroids and producing hyperplasia of the endometrium through their prolonged effect.

The cause of bleeding in polyps needs little discussion. They are often multiple, frequently missed and not infrequently associated with myomas.

The term inflammatory usually includes the specific pelvic infections, gonorrhea, tuberculosis, and post-partum infections, as well as the more

innocent lesions, such as cervical erosion and vaginitis. The specific infections may cause bleeding by a local reaction in the endometrium or through an interference with the ovarian mechanism and a resulting dysfunction.

Erosions of the cervix undoubtedly are as capable of producing bleeding from the local lesions as any abrasive type of wound would do. An erosion of the cervix, however, may exist in a patient suffering from abnormal functional bleeding.

Malpositions such as retroversion and prolapse, do not cause bleeding unless there is a sufficient engorgement produced in the uterus through its position, which restrains blood return, or unless there is an associated functional effect on the endometrium.
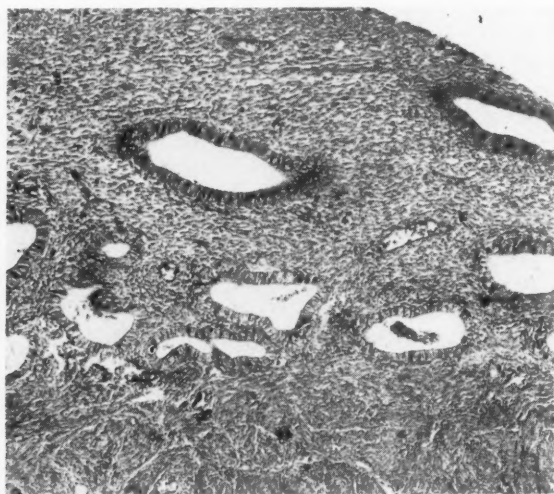
Fig. 1.—Flattened endometrium in state of hyperplasia overlying a fibroid (SC 2668). Patient had had menorrhagia for ten months; 21 days since last menstruation.

Blood dyscrasias are infrequently found associated with vaginal bleeding and might be considered as an organic cause. Kahn[15] reported 42 cases of blood dyscrasias of all types with 51.1 per cent having normal menstruation, 33.3 per cent having excessive and 15.5 per cent having diminished menstruation.

The Endometrial Patterns in Relation to Bleeding.—Abnormal bleeding may occur in patients with grossly normal pelvic organs with the endometrial pattern of a normal cyclical phase. Many terms are used to designate the phases of the normal cycle, but we have used the simple classification of early follicular phase, follicular phase, early corpus luteum phase, and premenstrual phase. Although the time of the cycle is usually easily recognizable, Evans and Swezy[16] maintain that premenstrual changes may occur immediately following menstruation and point out the hazards of comparing specimens, but Novak[17] feels that in the small percentage of cases of bleeding from secretory epithelium, the musculature may be at fault, or a vasomotor disorder affecting the vascular system may cause bleeding. Traut and Kuder[18] believe that an alteration of the corpus luteum phase may occur as a result of a weak but prolonged effect of the corpus luteum. As a result of their

studies of blood estrin, prolan titer, and the histology of the endometrium in a series of 97 cases, they decided that bleeding might be due to a mal-deciduation of the endometrium as a result of prolonged and exhausting secretory activity in the glandular elements and associated stromal changes. Anspach and Hoffman[19] found a large percentage of cases in each age group in bleeding from normal endometrium.

The term, *atrophic endometrium*, needs clarification. There certainly is a definite type of endometrial pattern associated with a hormonal decrease resulting from castration or aging, which can be considered an atrophic condition with decreased glandular elements in a thin endometrium. Novak[17] has described instances after the menopause where
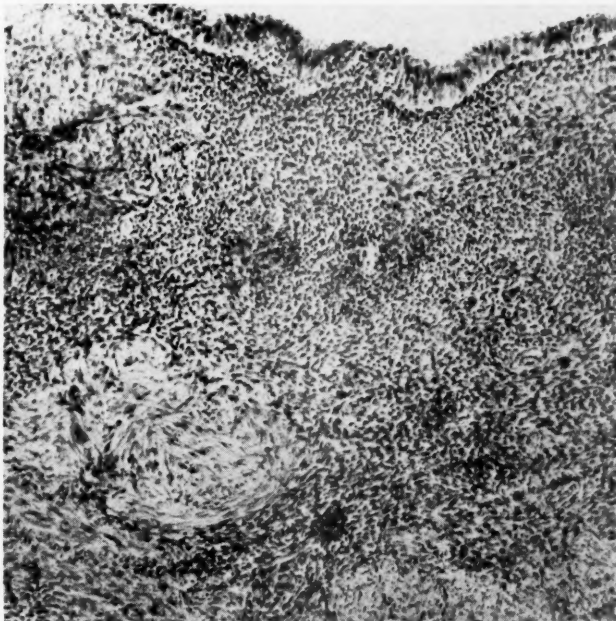
Fig. 2.—Atrophy and fibrosis (SB 8876).

cystic changes occur in this atrophic endometrium, indicating a hormonal imbalance as well as diminution. There is also, however, a mechanical type of "atrophy" found over a fibroid which is really a thinned or flattened endometrium. This may show any one of the normal cyclical changes on an abnormal form as hyperplasia (Fig. 1). A third type of atrophy may occur from a purely local uterine condition of endarteritis as seen in fibrosis uteri (Fig. 2).

The term *hyperplasia*, for which Novak popularized the phrase, "swiss cheese endometrium," has been too frequently described to need elaboration. Herrell[21] prefers the term cystic endometrium, feeling that the cystic formation is a result of an ovarian failure as it occurs in all phases of the endometrium. Randall and Herrell[22] found abnormal bleeding to occur in cystic endometrium associated with corpus luteum phase. However, it was noted only in the early corpus luteum phase. In their series cystic endometrium in late corpus luteum phase was not associated with abnormal bleeding. Most writers feel, however, it is produced by a prolonged and unopposed production of estrogenic hormone.

A condition of hypertrophy without hyperplasia exists when certain hormonal imbalances produce a decidual-like hypertrophy of the stroma cells without any glandular increase. Reinhart[23] described a case in which this progressed to a marked degree.

Adenomyosis may exist with the endometrial patterns in all the normal cycles as well as hyperplasia and atrophy. Not infrequently the islands do not react as does the rest of the endometrium.

As described by Kotz and Parker,[24] Graves,[25] Traut and Kuder,[18] Hamblen,[26] and Jones,[27] mixed endometrial patterns may contain secretory glands in a follicular stroma, or follicular glands in a secretory stroma, as well as both types of glands existing together. Fig. 3 shows a nonreacting cystic gland in corpus luteum phase endometrium.

Fig. 3.—Nonreactic cystic glands in typical secretory endometrium (SC 141). Patient, aged 45 years, had a fibroid and metrorrhagia for two months.

Although *chronic endometritis* does not entertain the popularity as a diagnosis that it did a decade ago, there is little doubt of the frequency of this endometrial pattern. The inflammation may be chronic with the characteristic round cell infiltration in any phase of the endometrial cycle, or actually an acute inflammatory process may exist.

Results

The cases of this series have been carefully reviewed and the most apparent cause for bleeding assigned to each. These are shown in Table II.

Complications of pregnancy occurred in 861 cases, or 21.8 per cent of the total, divided into age groups.

External cancer was a cause of bleeding in 611, or 15.4 per cent, of the 3,956 cases divided in age groups. Carcinoma of the ovary occurred in ten instances and in all age groups below fifty, but no endometrial slides were available to determine the cause of the bleeding.

TABLE II. ANALYSIS OF THE CAUSES OF BLEEDING IN 3,956 CASES

AGE BY DECADES	10-19	20-29	30-39	40-49	50
Pregnancy	38	472	306	45	0
Cancer					
Of uterus and vagina	9	29	268	271	34
Of ovary	1	2	3	4	0
Benign Tumors					
Fibroids, intramural and sub-serous	0	51	314	340	61
Submucous fibroids	0	1	14	136	·21
Fibroids and adenomyosis	1	0	13	0	0
Fibroids and ovarian tumors	0	0	25	3	2
Fibroids and polyps	1	2	6	21	6
Ovarian tumors	1	15	15	19	2
Endometrial polyps	0	4	6	12	3
Cervical polyps	1	5	15	17	1
Urethral polyps	0	3	0	0	0
Endometriosis alone	0	0	2	0	0
Inflammations					
Pelvic infections	34	367	205	53	4
Cervical erosions	7	100	70	33	5
Senile vag. itis	0	0	0	0	2
Malposition	2	44	22	5	0
Grossly Normal	8	84	107	163	20

TABLE III. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH FIBROIDS (INTRAMURAL AND SUBSEROUS)

AGE BY DECADES	20-29	30-39	40-44	45-49	50
Normal Endometrium					
Premenstrual	2	8	31	9	4
Early corpus luteum	5	25	0	0	0
Late follicular phase	13	14	24	20	13
Early follicular phase	2	5	3	4	0
Hormonal Changes					
Hypertrophy without hyper-plasia	2	0	1	0	0
Hyperplasia	3	8	12	10	3
Atrophy	0	1	4	3	6
Mixed endometrium	0	5	0	0	0
Flattened Endometrium					
Corpus luteum phase	0	1	1	0	0
Late follicular phase	1	2	0	0	2
Hyperplasia	0	1	0	0	0
Atrophy	0	0	0	0	1
Adenomyosis					
Corpus luteum phase	0	0	4	0	0
Late follicular phase	0	0	4	4	1
Hyperplasia	0	0	0	2	1
Inflammations					
Acute endometritis	0	1	1	0	0
Chronic endometritis	3	5	2	2	1

Fibroid tumors were found in 938 cases, of which 172 were submucous in location. Slides of the endometrium were available in 369 cases and these are the basis for Tables III and IV which show the different types of endometrial patterns for submucous and other fibroids. The 40 to 49 age group is divided because of the importance of this decade.

TABLE IV. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH SUBMUCOUS FIBROIDS

AGE BY DECADES	20-29	30-39	40-44	45-49	50
Normal Endometrium					
Premenstrual	0	0	8	7	3
Early corpus luteum	0	2	0	0	0
Late follicular phase	0	1	11	8	5
Early follicular phase	0	0	2	0	0
Hormonal Changes					
Hypertrophy without hyper-plasia	1	0	0	0	0
Hyperplasia	0	0	4	7	1
Atrophy	0	0	4	3	1
Mixed endometrium	0	0	0	1	0
Flattened Endometrium					
Corpus luteum phase	0	2	1	0	0
Late follicular phase	0	0	0	0	2
Early follicular phase	0	0	0	0	1
Adenomyosis					
Corpus luteum phase	0	2	2	1	0
Late follicular phase	0	0	1	1	0
Hyperplasia	0	0	1	0	0
Atrophy	0	0	1	2	0
Inflammations					
Chronic endometritis	0	1	1	0	1

Adenomyosis was found in association with fibroids in only 14 cases, but this undoubtedly represents a smaller figure than is actually the case, since numerous sections are necessary to exclude this possibility. Hyperplasia was noted in one case and atrophic endometrium in another. The remaining cases showed normal endometrial patterns in the different phases of the cycle.

Fibroids were found associated with polyps in 36 instances, these being distributed through all age groups but with the highest incidence between forty-five and forty-nine years of age. Only 17 of these cases had endometrial slides available for study, and of these 7 showed only the polypoid structure. The others were diagnosed as normal endometrium except for one case of flattened endometrium in early follicular phase and two cases of chronic endometritis.

We did not find evidence to support the view of Witherspoon[13] that the small follicular cysts were an integral part of the pathogenesis of myomas as they were absent in many instances and are, of course, known to be present in many cases not associated with fibroids. Therefore, we only included ovarian tumors over 3 cm. in diameter among the cases labeled as fibroids with ovarian tumor. Thirty such cases were noted with their principal number between 30 and 39 years of age. Ovarian tumors associated with fibroids were of the following types: dermoids, 5; corpus luteum cysts, 3; and retention, follicular, or serous cysts, 22. In only 8 cases were endometrial specimens available. Two dermoids were associated with late follicular phase, one corpus luteum cyst was associated with corpus luteum phase and the other endometrial patterns, associated with serous or follicular cysts, were early follicular phase, one; late follicular phase, two cases; atrophy, one case; and chronic endometritis, one case.

Fifty-two benign ovarian tumors were found, these being distributed in all age groups with the principal age incidence from twenty to twenty-nine. Again 3 cm. was taken as an index of cyst size to

eliminate the tiny follicular or retention cysts so common in cases without bleeding. The 19 cases with available endometrial and ovarian slides are classified in Table V.

TABLE V. BENIGN OVARIAN TUMORS AND ASSOCIATED ENDOMETRIAL HISTOLOGY

TYPE OF BLEEDING	AGE	PATH. NO.	OVARY	ENDOMETRIAL HISTOLOGY
Both	15	SB 8700	Simple cyst	Chronic endometritis
Metrorrhagia	25	SC 4827	Simple cyst	Follicular phase
Both	24	SC 3459	Simple cyst	Corpus luteum phase
Both	25	SC 3639	Simple cyst	Follicular phase
Metrorrhagia	27	SC 5179	Follicular cyst	Hypertrophy
Menorrhagia	26	SD 144	Simple cyst	Follicular phase
Both	24	SB 9466	Follicular cyst	Hypertrophy
Metrorrhagia	22	SD 2720	Corpus luteum cyst	Adenomyosis Follicular phase
Both	24	SC 2458	Corpus luteum cyst (right) Serous cyst (left)	Chronic endometritis
Metrorrhagia	24	SC 7146	Follicular cyst	Chronic endometritis
Both ·	26	SC 4332	Serous cyst	Hypertrophy without hyperplasia
Both	25	SC 8126	Serous cyst	Hypertrophy without hyperplasia
Menorrhagia	36	SC 797	Dermoid	Chronic endometritis
Menorrhagia	32	SC 1516	Hemorrhagic cyst	Corpus luteum phase
Menorrhagia	42	SC 3681	Serous cyst	Atrophic
Both	41	SB 2782	Corpus luteum cyst	Follicular phase
Metrorrhagia	44	SC 4303	Indefinite cyst type	Hypertrophy
Metrorrhagia	40	SC 5668	Indefinite cyst type	Follicular phase Hypertrophy
Menorrhagia	53	SD 2262	Serous cyst	Atrophic

Twenty-five endometrial and 39 cervical polyps were found, the cervical cases occurring in all age groups, while no endometrial polyps were found in the ten to nineteen age group.

No outstanding endometrial pattern was noted in either group among the cases with available slides.

In a sufficient number of these cases, histories were accurate enough to realize menorrhagia was not an infrequent type of bleeding.

Only two cases of endometriosis alone were found in our series and the patients were at 30 to 39 years and without endometrial studies.

TABLE VI. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH PELVIC INFLAMMATORY DISEASE

AGE BY DECADES	10-19	20-29	30-39	40-44	45-49	50
Normal Endometrium						
Premenstrual	0	2	1	4	1	0
Early corpus luteum	1	2	7	4	0	0
Late follicular phase	0	6	10	0	0	0
Early follicular phase	0	7	3	0	0	0
Hormonal Changes						
Hypertrophy without hyperplasia	0	9	0	0	0	0
Hyperplasia	0	1	2	2	0	0
Mixed endometrium	0	1	0	0	0	1
Adenomyosis						
Late follicular phase	0	0	0	1	0	0
Early follicular phase	0	0	0	1	3	0
Hyperplasia	0	0	0	0	1	0
Inflammations						
Chronic endometritis	1	23	3	11	0	0

This figure is undoubtedly misleading. The patient in whom endo-metriosis alone is a cause of bleeding is rarely operated upon, as it is frequently difficult to make such a preoperative diagnosis. Perhaps, had every one of the cases listed as grossly normal, or the mild chronic inflammatory cases been subjected to laparotomy, the pri-mary diagnosis of endometriosis would have been much higher.

There were 663 cases of bleeding associated with pelvic organs as the seat of inflammatory lesions due to an infectious process with the highest incidence between 20 and 29 years. Of these, 108 had avail-able slides and 38 of these showed an endometrial pattern of chronic endometritis. Table VII shows the endometrial patterns.

Among 215 cases of cervical erosions, enough histories revealed menorrhagia to cause some speculation as to the cause of bleeding being in the endometrial pattern rather than in the obvious organic lesion. The highest incidence in this group occurred between 20 and 29 years of age with a close second in the 30 to 39 age group. Only 95 had microscopic slides available for study. The endometrial pat-terns are shown in Table VI.

TABLE VII. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH CERVICAL EROSION

AGE BY DECADES	10-19	20-29	30-39	40-44	45-49	50
Normal Endometrium						
Premenstrual	0	4	2	4	1	0
Early corpus luteum	0	8	3	0	2	0
Late follicular phase	0	17	6	8	4	0
Early follicular phase	0	5	0	0	0	0
Hormonal Changes						
Hypertrophy without hyper-plasia	0	5	0	0	0	0
Hyperplasia	0	4	5	3	2	1
Atrophy	0	0	0	1	0	0
Adenomyosis						
Corpus luteum phase	0	1	0	0	0	0
Inflammation						
Chronic endometritis	1	5	1	2	0	0

TABLE VIII. ENDOMETRIAL HISTOLOGY ASSOCIATED WITH GROSSLY NORMAL PELVIC ORGANS

AGE BY DECADES	10-19	20-29	30-39	40-44	45-49	50
Normal Endometrium						
Premenstrual	0	8	1	18	16	2
Early corpus luteum	1	2	3	1	0	0
Late follicular phase	4	12	8	12	7	4
Early follicular phase	0	8	2	1	1	0
Hormonal Changes						
Hypertrophy without hyper-plasia	0	10	0	0	0	0
Hyperplasia	0	5	5	16	8	0
Atrophy	0	0	0	0	5	2
Mixed endometrium	1	0	1	0	0	0
Adenomyosis						
Late follicular phase	0	0	0	0	0	1
Early follicular phase	0	0	0	1	0	0
Inflammation						
Chronic endometritis	0	1	2	0	3	1

There were 73 patients with pronounced uterine malposition noted with the highest incidence between 20 and 29 years of age. Although only 33 cases had available endometrium these were enough to point out that no endometrial pattern is typical. All of the normal phases as well as the hormonal influence as portrayed by hyperplasia, and hypertrophy without hyperplasia, and the mixed endometrium were present. Chronic endometritis was noted in one instance.

Grossly normal pelvic organs were noted in 382 cases with slides available in 173 cases, as shown in Table VIII.

Discussion

From the above results we would like to offer the opinion that abnormal vaginal bleeding is not caused by any one organic pathologic condition or endometrial pattern, but rather it is a symptom frequently associated with one of these lesions and a principal one in bringing the patient to present herself for advice. Patients with these same lesions often present themselves with other symptoms than bleeding, just as a third group, having no symptoms, is never examined and the lesion is found at autopsy, or as a physical finding when examined for some other disease.

References

1. Weintraub, F.: Am. J. Obst. & Gynec. 36: 476, 1938.
2. Taylor, H. C., Jr., and Millen, R.: Am. J. Obst. & Gynec. 36: 22, 1938.
3. Keene, F. E., and Payne, F. L.: South M. J. 27: 108, 1934.
4. Rongy, A. J., Tamis, A., and Gordon, H.: Am J. Obst. & Gynec. 31: 300, 1936.
5. Shaw, W.: J. Obst. & Gynaec., Brit. Emp. 39: 816, 1932.
6. Shaw, W.: J. Obst. & Gynaec. Brit. Emp. 40: 257, 1933.
7. Meyer, R.: Am. J. Obst. & Gynec. 22: 697, 1931.
8. Seegar, G. E., and Jones, H. W.: Surgery 6: 368, 1939.
9. Burch, L. E.: Surg., Gynec. & Obst. 62: 373, 1936.
10. Morse, A. H.: Yale J. Biol. & Med. 6: 89, 1933.
11. Jones, I. F.: J. Arkansas M. Soc. 31: 109, 1934.
12. Faber, J. E.: Proc. Staff Meet. Mayo Clinic 11: 299, 1936.
13. Witherspoon, J. T.: Surg., Gynec. & Obst. 61: 743, 1935.
14. Twombly, G. H., and Millen, R. S.: Surg., Gynec. & Obst. 72: 605, 1941.
15. Kahn, M. E.: J. A. M. A. 99: 1563, 1932.
16. Evans, H. M., and Swezy, O.: Mem. Univ. California 9: 119, 1931.
17. Novak, E.: Cyclical Changes in Genital Canal. In: Obstetrics and Gynecology. Ed. by A. H. Curtis. Philadelphia, 1933, W. B. Saunders Co., 1: p. 306.
18. Traut, H. F., and Kuder, A.: Surg., Gynec. & Obst. 61: 145, 1935.
19. Anspach, B. M., and Hoffman, J.: Am. J. Obst. & Gynec. 28: 473, 1934.
20. Novak, E., and Richardson, E. H.: Am. J. Obst. & Gynec. 42: 564, 1941.
21. Herrell, W. E.: Am. J. Obst. & Gynec. 37: 559, 1939.
22. Randall, L. M., and Herrell, W. E.: Surg., Gynec. & Obst. 65: 666, 1937.
23. Reinhart, H. L.: Am. J. Clin. Path. 5: 365, 1937.
24. Kotz, J., and Parker, E.: Endocrinology 24: 447, 1939.
25. Graves, W. P.: Am. J. Obst. & Gynec. 20: 500, 1930.
26. Hamblen, E. C.: Endocrinology 20: 769, 1936.
27. Jones, H. W.: Am. J. Obst. & Gynec. 35: 64, 1938.

THE ASSOCIATION OF MILD EXTERNAL HYDROCEPHALUS WITH DEATH IN THE EARLY DAYS OF LIFE

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AN INCREASE in the amount of cerebrospinal fluid present within the intermeningeal spaces surrounding the brain which is associated with progressive, fatal respiratory distress in the newborn infant has not been previously recognized. We have been aware for some time that there is a small group of infants, usually delivered by cesarean section, who, although normal at birth, subsequently develop respiratory disturbances and fail to survive more than twelve or eighteen hours after birth. These infants almost invariably show a marked increase in intracranial fluid. We were originally of the belief that this increase in fluid occurred only following delivery by cesarean section, and although there is a high degree of correlation between the incidence of external hydrocephalus and cesarean section, we have recently observed similar clinical and pathologic findings when delivery has been by the vaginal route.

External hydrocephalus, the term generally used to indicate an increase in fluid around the brain, is infrequently observed and is in general a poorly defined entity. When present from birth it has been considered as possibly due to (1) intrauterine meningitis, either inflammatory or noninflammatory; (2) nonfunctioning of the mechanism controlling absorption of spinal fluid; (3) stasis caused by pressure on the blood and lymphatic channels of the neck; (4) hypoplasia of the cerebral hemispheres with a resulting compensatory fluid outflow. Shannon[1] believes that an increase in fluid around the brain may result from calcium deficiency and may be the immediate cause of the hyperirritability demonstrated by such patients.

External hydrocephalus has been described in the adult under the term serous or aseptic meningitis. It is essentially an edema of the leptomeninges in which the subpial and subarachnoid spaces are distended with fluid and the true criteria of inflammation are lacking. It has been observed following head trauma, infectious diseases, various intoxications, alcoholism, uremia, and intracranial tumors.

In the infant at birth the amount of fluid within the skull varies with the gestational age. We have reported measurements of this fluid in a previous publication,[2] and have found that with a birth weight exceeding 2,000 Gm. very little fluid can be demonstrated at autopsy in the majority of infants who die in the first few days of life.

In the infants to be described in this report a marked increase in the amount of intracranial fluid has been found within each skull, the measurable volumes ranging from 15 to 74 c.c. The meningeal vessels in such cases are raised from the surface of the brain and appear to float in fluid. After the cranial cavity is opened this fluid drains quickly from the brain surface and meninges and is consequently visible only in the freshly opened skull. Free fluid is usually observed in the cranial fossae after the brain has been removed.

The clinical histories of these infants are remarkably similar. Practically all breathe immediately after birth, and they are sent to the nursery as normal newborn infants. Within a short time, varying from a few minutes to a few hours, they develop respiratory distress which becomes progressively worse despite all therapeutic measures. Such infants usually breathe irregularly and with apparent difficulty, often with marked costal retraction. Cyanosis develops and frequently there is evidence of cerebral irritation in the form of a weak high-pitched cry, restlessness, muscle spasm, or even convulsions. A clinical diagnosis of atelectasis, pneumonia, congenital heart disease, or intracranial hemorrhage is usually made. At autopsy, however, it is rare to find definite pathologic lesions which are sufficient to explain satisfactorily the cause of death. Varying degrees of atelectasis are usually present but the alveolar nonexpansion is almost never primary in character, and instead is a result of the gradual resorption of air which takes place during the agonal period. The one pathologic condition which has been demonstrated in all of these infants is an amount of cerebrospinal fluid greater than that ordinarily seen.

Material

From our own hospital and from other institutions in the city we have observed 20 infants weighing over 2,000 Gm. who have had excessive amounts of fluid within the skull and who have shown a clinical course similar to that described above. Twelve were delivered by cesarean section; 8 were vaginal deliveries, 4 of which followed late artificial rupture of the membranes (breech 2, low forceps 2) and 4 of which followed spontaneous rupture of the membranes (natural cephalic 3, low forceps 1).

The infants delivered by cesarean section lived from five to thirty-five hours. Respiration was established promptly in 6 and in the other 6 was delayed, irregular, or shallow for five to ten minutes after birth, and in one instance remained so for one and one-half hours. All but one were considered normal infants on admission to the nursery. Following the establishment of normal respiration all twelve infants later developed respiratory distress. The symptoms prompted a clinical diagnosis of intracranial hemorrhage twice, congenital heart disease once, and congenital atelectasis in most of the remainder. Oxygen administration, drug stimulation, tracheal aspiration, and artificial respiration were of no avail. Autopsy revealed excessive intracranial fluid in

all, and, in addition, minimal early pneumonia in four instances, petechiae of the thoracic viscera in 2 and a small intraventricular clot within one cerebral hemisphere in 1. The amount of fluid within the head was measured in 7 cases. It varied from 15 to 73 c.c. with an average of 38.7 c.c.
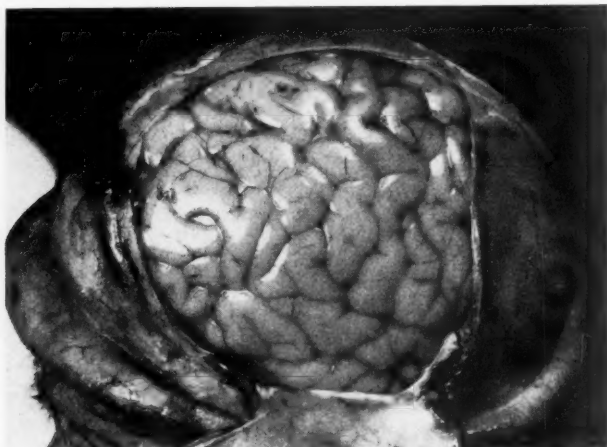

Fig. 1.—Skull opened by the Beneke technique showing normal convolutions and no visible fluid. Aged 13 hours, weight 2,600 Gm. Spontaneous cephalic delivery.
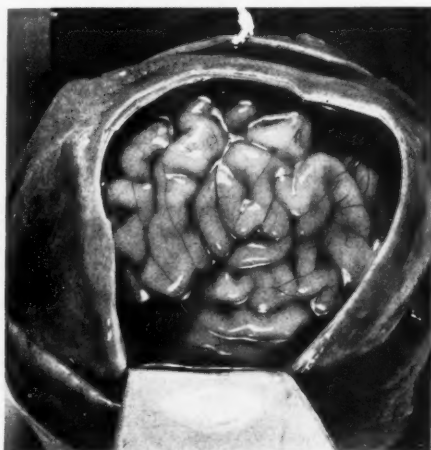
Fig. 2.—Skull opened by the Beneke technique showing marked increase in intracranial fluid. Forty-five cubic centimeters were measured. Aged 8 hours, weight 2,345 Gm. Cesarean section because of inadequate pelvic size.

The indications for the cesarean sections had been placenta previa 3, cephalopelvic disproportion or contracted pelvis 5, partial premature detachment of the placenta 1, rheumatic heart disease 1, elective section with sterilization 1, and incomplete rupture of the uterus one. The membranes were intact at the time of cesarean section in 10, with no record being available in the other 2. Three patients had had mild labor pains for three, four, and eight hours, respectively. The type of anesthesia included cyclopropane 5, ethylene 3, novocain 2, and unrecorded 2.

Of the 4 infants delivered following late artificial rupture of the membranes by methods other than cesarean section, two breathed spontaneously immediately after birth and appeared entirely normal. Respiration was delayed two minutes and a tracheal catheter was used in the third, and in the fourth respiration was never normally established. The last infant lived only one hour. The first three survived eighteen, forty-five, and fifty hours and the clinical course of each was similar to those dying after cesarean section. At autopsy there was slight interstitial pulmonary hemorrhage in 2 and no abnormality exclusive of increased fluid in the other 2. The amount of fluid within the head was 22, 30, 32, and 55 c.c. Labor lasted from four hours to seven and one-half hours. No significant maternal complications were present.

The 4 remaining infants were delivered after spontaneous rupture of membranes. Respiration was promptly established in 3, although it remained irregular or shallow for some time in 2 of these. In the fourth, respiration was slightly delayed but soon became normal. These infants lived three, twelve, thirteen, and eighteen hours and showed a repetition of the clinical findings noted in the previously described infants. Labor was less than six hours in 3, and thirty-three hours in the fourth. No maternal complications were present. At autopsy early pneumonia was found in one and petechiae of the thoracic viscera in 2. Fluid measurements were 22, 25, 40, and 74 c.c.

In addition to the 20 infants born alive, 5 others have been found who exhibited a marked increase in intracranial fluid. These died in the intra-partum period shortly before birth. One of these was delivered by laparotomy following rupture of the uterus which had resulted in extrusion of the infant into the abdominal cavity. The other 4 were delivered vaginally without instruments following artificial rupture of the membranes. Two of the infants were known to have been alive at the time of membrane rupture and the other two were alive at the last examination for heart tone prior to delivery. Membranes in these two were ruptured at the end of the first stage of labor. Labor lasted approximately three and one-half hours in 3 and sixteen hours in the fourth. Associated anatomic lesions demonstrable at autopsy were petechiae of the thoracic viscera (two) and clubfeet and a cleft palate (one). Fluid measurements in two of the cases were 35 and 37 c.c.

Discussion

The question immediately arises as to whether the excessive meningeal fluid is primary or secondary, i.e., whether it is the cause or the result of the asphyxia arising from inadequate pulmonary ventilation.

Clifford[3] believes that the meningeal edema is part of a progressive disturbance which is brought about by inadequate oxygenation of the blood. He has reported 11 infants who died following cesarean section performed for maternal hemorrhage from placenta previa. All infants developed severe respiratory embarrassment, and all but 2 died within thirty-six hours after birth, although no evidence of fetal distress had been noted prior to delivery. He believes that asphyxial changes resulting from interference with placental circulation had occurred before delivery despite the absence of symptoms. He states that the initial stage of generalized congestion which results from asphyxia is soon

followed by extravasation of fluid into organs and body cavities and that an accompanying subarachnoid accumulation of cerebrospinal fluid may be produced.

In support of this belief are the findings of Nicholson,[4] who has shown that dogs subjected to low alveolar oxygen concentrations for short periods of time exhibit a decrease in the flow of cerebrospinal fluid while exposure over longer periods tends to increase the flow. High carbon-dioxide concentrations also tend to increase the flow of fluid.

The clinical course and pathologic findings in the infants reported by Clifford are similar to those that we have described above. It is interesting to note that all were delivered by cesarean section in association with placenta previa, while in our series only three of the infants delivered by the same method were subjected to this procedure because of placenta previa. We have observed a large number of infants delivered through the vagina who have died following placenta previa and premature detachment of the placenta where death was definitely due to anoxia. Although there is often a slight extravasation of fluid and red blood cells into the meningeal spaces in such cases, the amount of fluid is rarely as great as that found following delivery by cesarean section. Our experience suggests that the method of delivery may be more important in the production of increased fluid than is the indication for the operation.

Why only certain infants should exhibit this increase in meningeal fluid is not clear. It occurs proportionately much more often in association with birth by cesarean section for these infants represent only about one-twentieth or less of all those born. In general infants delivered by this method vary from those born by the vaginal route only inasmuch as they are suddenly removed from the intrauterine environment, instead of being subjected to the pressure exerted by uterine contractions and the passage of the head through the birth canal. One could conceive that a greater amount of fluid than we ordinarily realize is present within the cranial vault during intrauterine life; that nature has provided it for protection during birth in order that molding of the skull may not cause damage to the brain substance; that normally it is reduced in amount during the process of birth, and that when the head does not pass through the pelvis, the amount normal to intrauterine life remains. On the other hand it could also be possible that relatively little fluid is present while the infant is within the uterus, but that when suddenly removed, the reduction in pressure to which it is subjected, causes an extravasation of fluid into the spaces around the brain.

The group which is particularly affected is made up of those infants who are slightly premature and have a birth weight between 2,000 and 2,500 Gm. Of the 25 infants discussed in this report, 16 weighed from 2,000 to 2,500 Gm., 6 from 2,500 to 3,000, and only 3 were over 3,000 Gm.

Summary

Among infants who die early in the newborn period of apparently unknown causes, meningeal edema (external hydrocephalus) must be considered as a possible cause. It is most commonly found following delivery by cesarean section. The maternal complications necessitating this method of delivery do not seem to be causative factors. Slightly premature infants are more often affected than those born at term.

References

1. Shannon, W. R.: Arch. Ped. 48: 153, 1931.
2. Potter and Rosenbaum: AM. J. OBST. & GYNEC. 45: 701, 1943.
3. Clifford, S. H.: AM. J. OBST. & GYNEC. 39: 388, 1940.
4. Nicholson, H.: Am. J. Physiol. 99: 570, 1932.

BLOOD NUCLEOTIDES IN PREGNANCY AND IN THE TOXEMIAS OF PREGNANCY*

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IT HAS long been suspected that the hyperuricemia observed in the toxemias of pregnancy might be due to an alteration in uric acid metabolism.[1-6] However, little is known of the metabolic pathways leading to the formation of or to the destruction of uric acid in man. One is, therefore, forced to make certain assumptions as to the possible pathways of uric acid metabolism in order to study the etiology of eclampsia. Precursors of uric acid might, for instance, be either blood nucleotides, nucleosides, or other purines.

The blood nucleotides were first discovered by Bass,[7] in 1914, when he presented evidence for the existence of combined purines in human blood. The combined purine was present as a nucleotide, and it was confined mainly to the red blood cells. Adenine seemed to be the principal purine present.

A successful isolation of the nucleotides present in human blood has not been accomplished. However, Jackson,[8] in 1924, did succeed in isolating a mixture of nucleotides from human blood. After hydrolysis of this product adenine was isolated. It is now generally assumed that adenylic acid is the principal nucleotide present in human blood. The pyridine-adenine dinucleotides are present only in traces.[9]

Although Bass first showed that the nucleotides of the blood were present mainly in the red cells, it remained for Rothmann[10] and Buell[11, 12] to demonstrate a correlation between the nucleotide content of the whole blood and its hemoglobin content, the hematocrit and the red cell count. Allen, Lucia and Eiler[13] have also found this relationship to hold except in cases of leukemia.[13, 14]

The nucleotide nitrogen of the whole blood in various diseases besides the anemias and polycythemias has also been studied by Rothmann[10] and by Allen, Lucia, and Eiler.[13]   In general no alterations in the nucleotide nitrogen were observed which could not be correlated with changes in the red cell or white cell count.   There is, however, a suggestion in Rothmann's paper that the blood nucleotides may vary independently of the red cells in gout.

In eclampsia there are rapid changes in the blood uric acid levels. There might be, therefore, some correlation between the blood uric acid level and the blood nucleotide level in this disease which could be observed.   Therefore, to ascertain whether or not there is any such relationship between the blood uric acid levels and the blood nucleotides in normal pregnancy and/or in the toxemias of pregnancy the blood nucleotide nitrogen, the blood nucleoside plus free purine nitrogen, and the uric acid were determined in a series of nontoxemia cases and in several cases of toxemia.

Several methods for the quantitative determination of the blood nucleotides have been described[11, 15-17, 19, 20] or applied to this end[18] by different investigators.   The results obtained are summarized in Table I. The type of filtrate used in the analysis is indicated since Kerr and Blish[19] showed that higher values are obtained with trichloroacetic acid filtrates than with tungstic acid filtrates.

TABLE I.   NUCLEOTIDE NITROGEN OF HUMAN BLOOD AS DETERMINED BY VARIOUS INVESTIGATORS

NUMBER OF DETER- MINATIONS	SEX	FILTRATES	NUCLEOTIDE NITROGEN MG. % (MEAN VALUE)	INVESTIGATOR
6	–	Acetic acid, Sulfo- salicylic acid and uranium acetate	4.17	Tannhauser and Czoniczer[17]
5	–	Folin-Wu	3.9	Jackson[16]
6	F	Folin-Wu	3.2*	Buell and Perkins[15]
11	M	Folin-Wu	3.9*	Buell and Perkins[15]
1	–	Tungstic acid	3.15	Mozolowski[18]
2	–	Acetic acid	3.97 5.74	Mozolowski[18]
98**	–	Folin-Wu	3.5	Rothmann[10]
190***	F	Folin-Wu	4.3	Erickson and Okey[21]
?	–	Trichloroacetic	6.86	Kerr and Blish[19]
?	–	Tungstic acid	3.81	Kerr and Blish[19]
25†	M	Trichloroacetic	6.25*	Buell[11]
25††	F	Trichloroacetic	5.5*	Buell[11]
93‡	M	Trichloroacetic	5.0	Allen, Lucia, and Eiler[13]
31§	F	Trichloroacetic	4.9	Allen, Lucia, and Eiler[13]

*Calculated values based on the assumption that the blood nucleotide is mainly adenylic acid, containing 20.1 per cent nitrogen.
**An average of 98 pathologic cases.
***On 16 women.
†On 9 men.
††On 8 women.
‡On 76 pathologic cases.
§On 26 pathologic cases.

Materials and Methods

All the cases studied were in-patients in this clinic. The nontoxemias were mainly cases of normal pregnancy. Included in the series, however, is one case (J. F.) of vomiting in the ninth week of pregnancy (of interest because of the extremely low blood uric acid level); one case of hypertensive disease (F. P.); and one case of cardiac disease with inactive pulmonary tuberculosis (M. M.). Except for J. F., they were all in their last week of pregnancy when the blood samples were taken.

Blood samples from the toxemia cases were taken at the height of the disease and in a few cases samples were taken again during the puerperium.

The blood was removed from an arm vein in the usual manner and was transferred to a small bottle containing oxalate. Ten milliliters of blood were then immediately added to 40 ml. of 10 per cent trichloroacetic acid. This mixture was shaken and allowed to stand for twenty minutes before it was filtered. Blood nucleotide and blood nucleoside plus free purine nitrogen were determined on an aliquot of this filtrate by the method of Kerr.[20] Simultaneous uric acid determinations were made on tungstic acid filtrates by the direct method of Folin.[22] The hematocrit was determined by the Wintrobe[23] method.

Results and Discussion

The results of these analyses are summarized in Tables II and III. The mean value for the blood nucleotide nitrogen in normal pregnancy during the last week of pregnancy is 3.48 ± 0.67 (σ) mg. per cent, while in the toxemias of pregnancy the mean value is 3.65 ± 0.58 (σ). The t value for the difference between the means is 1.83. The t value should be greater than 2.06 for the difference between the two means to be significant.

These values for the blood nucleotide nitrogen are significantly lower than those reported by both Buell[11] in normal nonpregnant women

TABLE II. NUCLEOTIDE NITROGEN, NUCLEOSIDE PLUS FREE PURINE NITROGEN, URIC ACID NITROGEN AND HEMATOCRIT OF NONTOXEMIC PATIENTS

CASE	HEMATOCRIT %	NUCLEOTIDE NITROGEN MG. %	NUCLEOSIDE + FREE PURINE NITROGEN MG. %	URIC ACID NITROGEN MG. %
I. S.	39	3.89	0.73	0.90
J. F.	39	3.11	—*	0.13
M. B.	35	3.22	0.59	0.71
F. P.	46	4.44	1.04	1.00
C. M.	38	3.22	0.95	0.90
F. P.	46	4.14	0.53	0.90
C. R.	32	4.06	1.42	1.02
E. V.	36	3.14	0.70	0.69
A. B.	39	3.58	0.84	0.90
D. R.	35	1.76	0.84	0.90
C. L.	38	3.42	1.26	1.31
A. G.	35	3.87	0.70	0.85
M. M.	41	3.42	0.70	1.42
Mean	35.9	3.48		

*Very low.

and by Allen, Lucia, and Eiler[13] in various diseases. Probably this difference is due to the decrease in both the hematocrit and hemoglobin usually observed in the last trimester and at term in normal pregnancy.[24] This contention is confirmed by the fact that the average hematocrit was 35.9 in the nontoxemic series and 35.2 in the toxemic series, while the normal nonpregnant hematocrit as given by Buell in her series would be about 42. The hemoglobin at term is usually about 80 per cent.[24]

TABLE III. NUCLEOTIDE NITROGEN, NUCLEOSIDE PLUS FREE PURINE NITROGEN, URIC ACID NITROGEN AND HEMATOCRIT OF TOXEMIA CASES

CASE	HEMATO-CRIT %	NUCLEO-TIDE NITROGEN MG. %	NUCLEO-SIDE + FREE PURINE NITROGEN MG. %	URIC ACID NITROGEN MG. %	DIAGNOSIS
J. W.	34	3.72	2.04	1.8	Mild pre-eclampsia
C. M.	36	3.64	1.26	1.4	Mild pre-eclampsia
E. A.	30	2.72	1.12	1.41	Toxemia
D. L.	41	3.78	1.26	1.5	Severe pre-eclampsia
H. S.	47	3.10	1.60	1.3	Severe pre-eclampsia
H. S.	–	4.53	1.74	0.9	H. S., 7 days post partum
O. P.	36	4.08	–	1.5	Severe pre-eclampsia
M. P.	41	3.24	2.19	1.60	Severe pre-eclampsia
M. P.	–	3.28	0.62	–	M. P., 7 days post partum
T. M.	39	4.94	0.84	1.4	Severe pre-eclampsia
P. F.	26	3.24	1.18	1.0	Severe pre-eclampsia
R. L.	36	3.67*	2.49	1.4	Post-partum eclampsia
(J. L.)	32	(3.95)†	4.02	3.4	Ante-partum eclampsia
H. M.	36	3.88‡	1.76	1.7	Fulminating eclampsia
(H. M.)	–	(3.36)§	1.18	1.7	Immediately post partum
H. M.	25	3.22	1.03	1.3	H. M., 4 days post partum
Mean	35.3	3.65			

*Delivery 7:12 A.M. Convulsion at 12:00 NOON. Blood sample at 12:15 P.M.
†Last convulsion 8:50 A.M. Blood sample at 10:00 A.M.
‡Last convulsion at 5:30 P.M. Blood sample at 7:15 P.M.
§Delivery 6:30 A.M. Blood sample 11:00 A.M.
Figures in parentheses were not included in the statistical evaluation of the data.

There seems to be no correlation between the blood uric acid level and the blood nucleotide level either in the nontoxemic or in the toxemic series. In this respect specific cases are of interest. Case J. F. in the nontoxemic series had an extremely low blood uric acid and yet here blood nucleotide nitrogen was within normal limits. In the toxemic series, it can be seen that the blood uric acid in Cases M. P., J. L., and H. M. were all quite high while the blood nucleotide nitrogen was again within normal limits.

These data agree in general with those obtained by previous investigators[10, 13] who have not found any significant variation in the blood nucleotides except in those diseases which involve the cellular elements of the blood. It is of interest to note in this connection that the concentration of the pyridine-adenine dinucleotides remains constant within the red cell even in pellagra.[9]

The nucleoside plus free purine nitrogen is of the same order of magnitude and in most cases approximately equals the value for the uric

acid nitrogen obtained by independent determinations of the uric acid by the Folin direct colorimetric method. Assuming that the methods used are sufficiently reliable, it would appear that nucleosides and purines other than uric acid are present in very small quantities in human blood.

Summary

The average blood nucleotide nitrogen in 12 cases of nontoxemic pregnancy with an average hematocrit of 36 per cent was 3.48 mg. per cent. There was no significant difference between this mean and the average blood nucleotide nitrogen determined in 12 cases of toxemias of pregnancy. The nucleoside plus free purine nitrogen was in most cases approximately equal to the uric acid nitrogen.

References

1. Stander, H. J., Duncan, E. E., and Sisson, W. E.: Bull. Johns Hopkins Hosp. 36: 411, 1925.
2. Stander, H. J., and Radelet, A. H.: Bull. Johns Hopkins Hosp. 38: 423, 1926.
3. Stander, H. J., and Cadden, J. F.: Am. J. Obst. & Gynec. 28: 856, 1934.
4. Cadden, J. F., and Stander, H. J.: Am. J. Obst. & Gynec. 37: 37, 1939.
5. Schaffer, N. K., and Stander, H. J.: Proc. Soc. Exper. Biol. & Med. 45: 180, 1940.
6. Crawford, M. D.: J. Obst. & Gynaec. Brit. Emp. 48: 60, 1941.
7. Bass, R.: Arch. exper. Path. u. Pharmakol. 76: 40, 1914.
8. Jackson, H., Jr.: J. Biol. Chem. 59: 529, 1924.
9. Klein, J. R., Perlzweig, W. A., and Handler, P.: J. Biol. Chem. 145: 27, 1942.
10. Rothmann, H.: Ztschr. ges. exper. Med. 77: 22, 1931.
11. Buell, M. V.: J. Biol. Chem. 108: 273, 1935.
12. Buell, M. V.: J. Biol. Chem. 112: 523, 1935-36.
13. Allen, F. W., Lucia, S. P., and Eiler, J. J.: J. Clin. Investigation 15: 157, 1936.
14. Allen, F. W., Lucia, S. P., and Eiler, J. J.: Proc. Soc. Exper. Biol. & Med. 34: 609, 1936.
15. Buell, M. V., and Perkins, M. E.: J. Biol. Chem. 76: 95, 1928.
16. Jackson, H., Jr.: J. Biol. Chem. 57: 121, 1923.
17. Tannhauser, S. J., and Czoniczer, G.: Ztschr. physiol. Chem. 110: 307, 1920.
18. Mozolowski, W.: Biochem. Ztschr. 206: 150, 1929.
19. Kerr, S. E., and Blish, M. E.: J. Biol. Chem. 98: 193, 1932.
20. Kerr, S. E.: J. Biol. Chem. 132: 147, 1940.
21. Erickson, S. E., and Okey, R.: J. Biol. Chem. 91: 715, 1931.
22. Folin, O.: J. Biol. Chem. 101: 111, 1933.
23. Wintrobe, M. M.: J. Lab. & Clin. Med. 15: 287, 1929.
24. Javert, C. T., Macri, C., and Kuder, K.: Am. J. M. Sc. 205: 399, 1943.

THE INCIDENCE OF THE RH FACTOR AND ERYTHROBLASTOSIS FETALIS IN CHINESE*

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RECENT studies have revealed that iso-immunization of the Rh– mother by the dominant Rh factor of fetal blood is the essential feature in the pathogenesis of erythroblastosis fetalis, in at least 90 per cent of the cases. The statistical data indicate that the source of the intrauterine hemolysis of fetal blood, which is responsible for the clinical and pathologic criteria of erythroblastosis fetalis, is the action of maternal immune anti-Rh agglutinins on the susceptible Rh+ fetal blood.[1, 2]

There is already evidence that the incidence of the Rh factor is different in the white and in the colored races. Thus, with a particular human anti-Rh serum, there are 15 per cent Rh– white individuals in contrast to values varying from 5 to 8 per cent among colored individuals.[3, 4] All other factors being equal, but particularly the capacity to produce anti-Rh agglutinins, one should expect to find a greater incidence of erythroblastosis fetalis in white than in colored infants.[3] This observation seems to correspond with clinical observations of Potter,[5] and our own recent experience with a vast clinical material. In postmortem studies of fetal and neonatal conditions, Potter found that the incidence of erythroblastosis fetalis was 2.1 per cent and 0.7 per cent for the white and colored races respectively.

Recently an opportunity presented itself to study the distribution of the Rh factor in Chinese living in New York City. In the course of a discussion, one of us (H. W.) expressed the opinion that this condition is probably rare among Chinese infants. If this could be shown to be correct, one should expect to find a very low incidence of Rh– individuals in a random Chinese population. This was confirmed in a study of 150 Chinese persons residing in New York City, only one of whom was Rh–. The contrasting distribution of Rh+ and Rh– reactions among white and Chinese as tested with three varieties of human anti-Rh sera is given in Table I.

TABLE I. AGGLUTINATION REACTIONS WITH HUMAN ANTI-RH SERA

NUMBER TESTED	ANTI-RH$_{1, 2}$		ANTI-RH$_1$		ANTI-RH$_2$	
	+	–	+	–	+	–
334 White	87.0	13.0	85.0	15.0	73.0	27.0
150 Chinese	99.3	0.7	99.3	0.7	93.0	7.0

In agreement with Landsteiner and Wiener the terminology used in Table I is employed for the differentiation of the three varieties of human anti-Rh sera. It is based on the observation of Levine[6] that the anti-Rh serum$_{1, 2}$ contains more than one antibody.

As indicated elsewhere,[2] anti-Rh$_{1, 2}$ or anti-Rh$_1$ sera are of far greater significance for the diagnosis of erythroblastosis fetalis than the anti-Rh$_2$ serum. Using the anti-Rh$_1$ serum which may be considered as standard, Rh– individuals are 21 times less frequent in Chinese than in white individuals. Accordingly, this observation serves as a basis to support the contention that erythroblastosis fetalis is very rare among Chinese infants. A search of the literature, indeed, reveals only one genuine case of erythroblastosis fetalis in a Chinese infant reported in 1932 by Ku and Li.[7] The files of the *Chinese Medical Journal* from 1916 to date fail to reveal the report of any other proved cases.

Further support for the view that erythroblastosis fetalis is very rare among Chinese infants could be obtained from the experience of Drs. N. J. Eastman[8] and U. Eno.[9] In the six years of his experience at the Peiping Union Medical College covering 4,000 deliveries, Dr. Eastman "saw no cases which were recognized as erythroblastosis fetalis," and he states further that none were observed in 3,000 additional deliveries in the four years subsequent to his stay in China. Dr. Eastman writes: "Of course, the question can be raised as to whether some instances of erythroblastosis fetalis were not overlooked. This is doubtless a possibility, but I believe that clear-cut examples of fetal hydrops could not have escaped our attention. In other words, my experience would be in keeping with your findings."

The experience of Dr. U. Eno, Professor of Obstetrics at the Woman's Christian Medical College in Shanghai, may also be quoted: "Mild jaundice of the newborn is very common in China, but no case of erythroblastosis fetalis was diagnosed or suspected in a series of 10,000 deliveries over a period of eleven years at the Margaret Williamson Hospital. This refers to the three well-recognized clinical forms of erythroblastosis fetalis: fetal hydrops, icterus gravis and anemia of the newborn."

Based on the incidence only of fetal hydrops of 1:1,348 deliveries as given by Javert,[10] one should expect at least 12 cases among 17,000 deliveries, the combined experience of Drs. Eastman and Eno. The incidence of all forms of erythroblastosis fetalis in New York is given as one in 400 deliveries, so that one may expect to observe more than forty cases in 17,000 deliveries. Granting that the milder forms of icterus gravis or anemia may have been overlooked, this should certainly not hold for fetal hydrops and the more severe forms of icterus gravis, the diagnostic criteria for which are, as a rule, clear-cut.

In a recent paper, Landsteiner, Wiener and Matson[11] found only one out of 120 full-blood American Indians to be Rh– in tests with standard anti-Rh sera. Accordingly, one should expect a correspondingly low

incidence of erythroblastosis fetalis also in American Indians, but clinical evidence to support this view is still to be supplied.

The bloods of Chinese and pure-blooded Indians, however, differ in the incidence of reactions obtained with the anti-Rh_2 serum. This is indicated in the results shown in Table II.

TABLE II

AUTHOR	RACE	NO. OF INDIVIDUALS	PER CENT	
			+	−
Levine et al.[2]	White	334	73	27
Landsteiner et al.[11]	Indians	69	58	42
Levine and Wong	Chinese	150	93	7

As already stated, the anti-Rh_2 serum is not as significant for the diagnosis of erythroblastosis fetalis and for the prevention of intragroup transfusion reactions as the anti-$Rh_{1,2}$ or anti-Rh_1 sera. However, these findings as well as these given in Table III are of considerable interest from an anthropological viewpoint.

The bloods of the Chinese individuals were tested also for the incidence of blood groups, subgroups and the factors M and N. For comparative purposes the corresponding distribution in a white population is also reported.

TABLE III

	WHITE	CHINESE
O	45.0	30.0
A	41.0	34.0
B	10.0	25.3
AB	4.0	10.7
M	29.2	23.3
N	21.2	22.0
MN	49.6	54.7

Of the 67 Chinese bloods of Groups A and AB, all but 9 were tested for the subgroups.* Only two of the 58 bloods, both in Group AB, were found to belong to subgroup A_2. In contrast to the low value of 3 per cent A_2 are the corresponding figures of 37 per cent for colored and 14 per cent for white individuals.[12]

Summary and Conclusion

Hitherto studies on the distribution of the blood groups and other blood factors in various races had academic interest only. However, this state of affairs is considerably altered by the findings presented on the correlation of the incidence of erythroblastosis fetalis and Rh negative reactions obtained with anti-Rh $serum_{1,2}$ or anti-Rh_1. The possibility of this relationship for the colored and white races was already suspected but it is definitely established on the basis of the more striking differences between white and Chinese population.

*These bloods were tested in four batches. One of these containing 9 individuals of Groups A and AB was not tested for the subgroups.

References

1. Levine, Ph., Katzin, E. M., and Burnham, L.: J. A. M. A. **116**: 825, 1941.
2. Levine, Ph., Burnham, L., Katzin, E. M., and Vogel, P.: Am. J. Obst. & Gynec. **42**: 925, 1941.
3. Levine, Ph.: Science **96**: 1452, 1942.
4. Landsteiner, K., and Wiener, A. S.: J. Exper. Med. **74**: 309, 1941.
5. Potter, E.: J. A. M. A. **115**: 996, 1940.
6. Levine, Ph.: New York J. Med. **42**: 1928, 1942.
7. Ku, D., and Li, Y.: Virchows Arch. f. path. Anat. **283**: 62, 1932.
8. Eastman, E. J.: Personal communication.
9. Eno, U.: Personal communication.
10. Javert, C.: Am. J. Obst. & Gynec. **34**: 1042, 1937.
11. Landsteiner, K., Wiener, A. S., and Matson, G. A.: J. Exper. Med. **76**: 73, 1942.
12. Landsteiner, K., and Levine, Ph.: J. Immunol. **18**: 87, 1930.

RHEUMATIC HEART DISEASE

A Controllable Complication of Pregnancy

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IN 1941 an analysis of 345 cases of rheumatic heart disease complicated by pregnancy was reported.[1] This series included all the cases seen at the Margaret Hague Maternity Hospital from January, 1933 to January, 1939. A second series including all the cases seen from January, 1939, to August, 1942, has recently been completed. This latter group comprises 223 cases.

In both series we followed the New York Heart Association classification as follows:

Grade I: Patients with cardiac disease and no limitation of physical activity.

Grade II: Patients with cardiac disease and slight limitation of physical activity.

Grade III: Patients with cardiac disease and marked limitation of physical activity.

Grade IV: Patients with cardiac disease who are unable to carry on any physical activity without discomfort.

From the analysis of the first series, there emerged three prognostic aids. We felt that it was possible to foretell fairly accurately which patient with heart disease will fail unless adequate bed rest is enforced. First, the functional capacity of the heart in the nonpregnant state is of great importance. In the first series 83 per cent of the failures occurred in the badly incapacitated groups, Grades III and IV, while only 17 per cent of the failures were in the comparatively well-functioning Grades I and II. Second, an equally important aid is the patient's age; 42.6 per cent of the pregnancies in women over thirty years of age were complicated by cardiac failure as compared to 16.1 per cent in the group under thirty. A third significant aid in prognosis is the

presence or absence of a history of previous failure. Of those that de-
compensated before, 75 per cent had cardiac failure when pregnant,
as compared to a 14.1 per cent incidence of cardiac failure in the group
who had never before experienced decompensation.

From the study of this first group of 345 cases several other conclu-
sions relative to the management of heart disease in pregnancy were
reached. It appeared that the greatest incidence of failure occurred
in the seventh and eighth months. It was found that the morbidity
and mortality rates following cesarean section were significantly higher
than following vaginal delivery, and that decompensation in labor was
a rarity.

Thus from Jan. 1, 1939, the cardiac clinic in the Margaret Hague
Maternity Hospital has been conducted on the following basic principles:

1. All pregnant women with heart disease are examined at frequent
intervals and urged to spend several hours in bed every day.

2. All patients whose measure of functional capacity prior to the
pregnancy places them in Grades III or IV are hospitalized at their first
visit to the clinic, regardless of how well they may seem to be at the
time; and kept at absolute bed rest for the remainder of the pregnancy.

3. All patients who give a history of previous decompensation are
treated as Grade III and IV cardiacs; hospitalization at absolute bed
rest for the remainder of the pregnancy, with no attention paid to their
functional capacity at the time first seen.

4. The cardiac patient who is more than twenty-five years of age is
observed at weekly intervals. At the first sign of any decrease in cardiac
reserve she is hospitalized and placed at absolute bed rest for the re-
mainder of her pregnancy.

5. Special care was taken and increased bed rest ordered in every
cardiac patient during the sixth, seventh, and eighth months.

6. Surgical intervention was considered contraindicated. Labor was
allowed to occur spontaneously and cesarean section resorted to only
when obstetric indications existed.

The purpose of this paper is to compare the result of this type of
management to that previously enforced. For this study we have
divided our cases into three groups, clinic cases, non-clinic cases, and
private cases. The clinic cases, a total of 157 patients, include all preg-
nant women with rheumatic heart disease who registered at the Mar-
garet Hague clinic at any time prior to delivery. The nonclinic cases,
a total of 11, are composed of that group of women who did not register
at the hospital until labor began or who were found to be in cardiac
failure at their first ante-partum clinic visit. The private cases made
up a total of 55 patients. Thus these three groups include every preg-
nant patient with rheumatic heart disease seen at the hospital from
Jan. 1, 1939, to Aug. 1, 1942.

In the clinic group of 157 consecutive cases there occurred four fail-
ures, an incidence of 2.5 per cent as compared to an incidence of 22.3
per cent in the first series. Only one death occurred in this group, an

incidence of 0.64 per cent as compared to an incidence of 3.47 per cent in the first series.

TABLE I. PRIVATE, CLINIC, NON-CLINIC CASES

	NONCLINIC	PRIVATE	CLINIC
Total	11	55	157
Failed	6, 54.5%	19, 34.5%	4, 2.5%
Died	2, 18.2%	5, 9.1%	1, 0.64%

We believe that several of the cardiac failures could have been avoided and therefore include a brief summary of the histories of these cases.

CASE 1.—C. S. (History 41307), aged 24 years, para i, gravida ii, had rheumatic heart disease with enlarged heart, mitral stenosis and insufficiency, Grade III prior to this pregnancy, and a history of decompensation in her first pregnancy. At the first clinic visit in the fifth month of her pregnancy, this patient was hospitalized and placed at absolute bed rest although her condition at the time seemed excellent. Her course in the hospital was so good that an order was left to "allow bathroom privileges." It should be stressed that this procedure was contrary to our general rules. Acute left ventricular failure occurred during the thirtieth week of this pregnancy. Response to therapy was good, compensation returned rapidly and spontaneous uneventful labor occurred ten weeks later.

CASE 2.—McN. (History 16727), aged 32 years, had rheumatic heart disease, enlarged heart, mitral insufficiency and stenosis, Grade III prior to this pregnancy, a history of previous decompensation. This patient, too, was admitted to the hospital in good condition at her first clinic visit in the third month of her pregnancy. Absolute bed rest was enforced for three months. This patient and Case 1 were in the hospital at the same time. This patient, too, was allowed "bathroom privileges" and she, too, failed at the beginning of the eighth month, an acute left ventricular failure, and died within twenty-four hours.

These two cases were grouped together because their histories are quite similar. They were in the hospital at the same time and received the same management. It was determined later that both patients had been allowed out of bed much more than the "bathroom privileges" had intended. Whether or not these failures could have been prevented is impossible to say, but an element of doubt exists and since this experience no compromise on bed rest is accepted. Absolute bed rest is strictly enforced.

CASE 3.—J. R. (History 43373), aged 22 years, had rheumatic heart disease, a small heart, mitral insufficiency, and stenosis, Grade I prior to this pregnancy. This patient was seen on a routine clinic visit and judged to be doing well. One week later, in the sixth month of her pregnancy, she was admitted in acute cardiac failure. The history revealed a day-long argument with her mother-in-law accompanied by

much emotional stress. Response to therapy was good. Spontaneous and uneventful labor occurred at term.

This failure was an unexpected and probably an unavoidable occurrence.

CASE 4.—M. D. (History 1145), aged 35 years, had rheumatic heart disease, enlarged heart, mitral insufficiency and stenosis, Grade III prior to this pregnancy. She was hospitalized at her first clinic visit in relatively good condition. Uncooperative to an extreme degree, she signed her release after five weeks of bed rest, did not report to clinic, and returned to the hospital six weeks later. A spontaneous two-hour labor was followed an hour later by acute left ventricular failure which responded quickly to therapy.

We anticipated trouble in this type of case and possibly could have avoided it. We believe that three of these failures were preventable.

In the private series of 55 patients there were 19 failures, an incidence of 34.5 per cent, and 5 deaths, or 9.1 per cent. While we do not intend to compare the private and clinic groups, we feel that the record made by the private doctor is a bad one. Many of the patients in the private series did not know they had heart disease; scarcely any received adequate bed rest; practically all revealed in their histories that their cardiac reserve had been decreasing gradually for weeks or months before frank decompensation had occurred, but the signals were unheeded. In the first series reported in 1941, the failure rate in the private cases was 45.2 per cent. Slight, if any, improvement has taken place.

The nonclinic group of 11 cases needs little comment. Six failures, 54.5 per cent, and two deaths, 18.2 per cent, occurred.

Since completion of the analysis of the first series of cases it has been the policy at the Margaret Hague Maternity Hospital to manage the labor of pregnant women with heart disease on the basis of obstetric

TABLE II.   CESAREAN SECTION, PRIVATE VS. CLINIC

GRADE	TOTAL	VAGINAL DELIVERY	CESAREAN SECTION
Clinic			
I	111	109	2
II	25	25	0
III	20	20	0
IV	0	0	0
	156	154	2
		98.7%	1.3%
Died undelivered 1			
Private			
I	40	35	5
II	9	7	2
III	3	3	0
IV	1	0	1
	53	45	8
		84.9%	15.1 %
Died undelivered 2			

indication, essentially as though the women were not suffering from heart disease. In short, heart disease ''per se'' is not an indication for cesarean section. In the present series of 223 cases, 10 sections were performed, an incidence of 4.6 per cent. However, the figures are more revealing when the private and clinic cases are compared.

Of the total of 156 clinic cases (the patient who died being undelivered), two sections were performed. One was considered necessary by the attending obstetrician in an elderly primipara with cephalopelvic disproportion. This patient was a well-compensated Grade I cardiac. The other was performed as an elective procedure at thirty-seven weeks' gestation because of toxemia of pregnancy. This patient was a well-compensated Grade I cardiac, a primipara with a breech presentation. Thus of the clinic series 98.7 per cent were delivered vaginally and 1.3 per cent by cesarean section, the latter by reason of obstetric indication.

Of the 53 private cases, two having died undelivered, 8, or 15.1 per cent, were delivered by the abdominal route. Two of these were performed at the moment of death in an effort to save the infants and should be discounted; 2 others were indicated by cephalopelvic disproportion; 1 was done for placenta previa; and 1, the Grade IV cardiac, was a previous cesarean section with twins and an embarrassing polyhydramnios in the present pregnancy. This leaves only 2 sections done for so-called cardiac indications. However, 4 other cesarean sections were performed with heart disease as the indication, but these could not be included in this analysis, since there was no good evidence on the chart to show whether or not organic heart disease existed. Thus at least 6 women out of 57 cases received operative interference by the private physician under the indication of heart disease.

We wish to emphasize that no patient in this entire series had her pregnancy terminated in the early months by medical or surgical means. In the clinic group all pregnancies were allowed to go to term; 9 labors were premature spontaneously, and there was one spontaneous abortion.

Summary and Conclusions

1. Two hundred twenty-three cases of pregnancy complicated by heart disease are reported.

2. A system of management of heart disease in pregnancy is briefly outlined. Absolute bed rest for certain classes of cardiac patients is stressed. By this means alone the incidence of decompensation in pregnant women with heart disease has been reduced from 22.3 per cent to 2.5 per cent, 4 cases out of the total of 157; and 3 of these failures may have been preventable. The mortality rate has dropped from 3.5 per cent to 0.64 per cent. If only part of the difference between the failure incidence in private and clinic cases, 34.5 per cent to 2.5 per cent, and if only part of the difference in mortality rates between these two groups of cases, 9.1 per cent to 0.64 per cent, is due to financial difficulties encountered by application of this therapy in private cases, some plan must be instituted by maternity hospitals and the associated communities to overcome such difficulties. However, the private doctor plays a most important part, too, and his responsibility in this condition must be stressed.

3. Heart disease is no indication for cesarean section. The two sections performed in the clinic series of 157 cases were on the basis of obstetric indication.

4. Considering a previous report of 345 cases together with this series of 223 cases, in which no therapeutic abortion was performed, it is probable that practically every pregnancy encountered in a patient with heart disease can be brought to a successful spontaneous termination, if adequate prenatal care is instituted and if absolute bed rest is enforced when indicated.

Reference

1. Gorenberg, H., and McGeary, J.: AM. J. OBST. & GYNEC. 41: 44, 1941.

126 GIFFORD AVENUE

CERVICAL SECRETION IN CHRONIC GONORRHEA IN THE PROSTITUTE

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IT IS well known that in the female chronic gonorrhea is sometimes difficult and occasionally impossible to diagnose. The so-called "stigmata" of chronic gonorrhea in the lower genital tract of the female are absent in some cases which are bacteriologically positive for the gonococcus. The majority of the cases of chronic gonorrhea in the female do, in our experience, bear clinical evidence of infection, though these clinical findings are not pathognomonic of gonorrhea and when present before treatment, may persist after gonococci have disappeared from the secretions.

The diagnosis of gonococcal infections by means of cultures is a great advance, but the culture method also has definite limitations, especially in chronic gonorrhea.

In 1942, a detailed clinical and bacteriologic study was made of the discharges from the cervix and urethra of 81 women, all prostitutes, who had been sent into the Kingston Avenue Hospital for the treatment of gonorrhea.

Material

The venereal disease service of the Kingston Avenue Hospital receives patients who have been found gonococcus positive by the Health Department. Because of their occupation (prostitutes), they have been forced to enter the hospital for treatment to render them noninfectious. The diagnosis of gonorrhea had been established in each case by a positive culture report from the Routine Gonococcus Culture Labora-

tory of the New York City Department of Health. No patient was sent in on a diagnosis of "clinical gonorrhea" or on positive smears alone.

Each of these patients had been examined gynecologically by a Health Department physician for clinical evidence of venereal infection. Twenty-four of the 81 cases, or 30 per cent, had been recorded on the basis of this examination, as clinically positive for gonorrhea. From this single clinical examination, it appears that 70 per cent of these proved cases of gonococcal infection had no clinical signs of gonorrhea.

At the Kingston Avenue Hospital a gynecologic examination of each patient was made at least three times weekly. One of these examinations was made by the resident gynecologist, one by the attendant on service, and a third examination by another member of the visiting staff.

The examination of the urethra Skene's and Bartholin's glands, the uterus and adnexa, was performed in the usual manner but need not be described here. Because it is the cervix which is most often the seat of gonococcal infection, and the urethra, Skene's and Bartholin's glands are less often involved, we will confine this report to our observations of the secretion of the cervix. We employed the following procedure in obtaining cervical secretion for examination: The cervix is exposed by means of a bivalve speculum, and the appearance of the os, the quantity and nature of secretion therefrom and also of vaginal secretion, if any, is noted. The external os is wiped clean with cotton balls. The blades of the speculum are then caused to come together compressing the entire vaginal portion of the cervix, and the speculum is drawn downward. Any secretion in the cervical canal is thereby forced out and is available for study.

The staff repeatedly examined cases together so as to arrive at an agreement as to descriptive terminology. The quantity and character of the cervical secretion was carefully observed at each examination. The quantity was designated as profuse, moderate, scant, or absent. In character, it was mucoid, purulent, or, in most cases, mucopurulent. In each case a saline suspension of the vaginal secretion was examined for trichomonads.

Findings Before Treatment

The records of the clinical examinations of some of our untreated cases showed fluctuations from time to time in the character and quantity of the discharge. At times profuse mucopurulent discharge was seen, then a day or two later the discharge might be described as scant, and some days later moderate, or again profuse. Repeated examinations on the same day showed fluctuations in the amount of discharge, but this might be ascribed to the expression of the secretion at the time of the previous examination. On some days there was no clinical evidence of infection, while at other times the evidence was unmistakable. In other cases, profuse purulent discharge was found persistently.

Of the 81 cases, in 58 (71.6 per cent) there was found at one time or another a profuse mucopurulent discharge from the cervix.

In 11 (14 per cent), the discharge was described as moderate. Therefore, 85 per cent of our cases repeatedly examined were found to have either moderate or profuse mucopurulent discharge from the cervix. In 12 cases scant or no abnormal cervical discharge was found at any of our examinations.

TABLE I. VARIATIONS IN CERVICAL DISCHARGE (WITHOUT TREATMENT)

	AD-MITTED											
1. L. G.	2/11	2/12 Prof.*	2/13 Scant	2/14 Scant								
2. W. H.	5/4	5/5 Scant	5/6 Prof.	5/11 Prof.	5/13 Mod.	5/15 Scant						
3. E. K.	4/25	4/27 Scant	4/29 Mod.	5/1 Mod.	5/4 Mod.	5/6 Prof.						
4. M. R.	2/18	2/19 Prof.	2/20 Mod.	2/21 Scant								
5. M. G.	3/2	3/2 Mod.	3/5 Scant	3/11 Mod.	3/14 Scant	3/23 Mod.	3/25 Scant	3/30 Prof.	3/31 Prof.			
6. A. C.	5/4	5/5 Prof.	5/6 Prof.	5/11 Prof.	5/13 Scant	5/15 Prof.						
7. B. C.	4/7	4/8 Prof.	4/10 Mod.	4/13 Mod.	4/15 Mod.	4/17 Scant	4/20 Prof.					
8. E. H.	3/26	3/28 Scant	3/30 Mod.	4/6 Scant	4/10 Mod.	4/13 Mod.	4/15 Mod.	4/17 Prof.	4/20 Scant	4/22 Scant	4/24 Prof.	4/25 Scant 4/27 Prof.

*Mod., moderate. Prof., profuse.

Clinical Examination

A single examination just before admission to the hospital had revealed clinical evidence of infection in only 30 per cent of our culturally positive cases of gonorrhea, as compared to 85 per cent when the patients were repeatedly examined while in the hospital.

There was a close correlation between the amount of gross cervical discharge and the number of pus cells in the smear. There were only four exceptions to this: In three cases the gross discharge was moderate while the number of pus cells was large. The fourth case showed profuse mucoid discharge with a complete absence of leucocytes on microscopic examination.

Gonococcus culture examinations are used not only for the diagnosis of gonococcal infections but also in the determination of cure. Since only culture positive cases are sent into Kingston Avenue Hospital for the treatment of gonorrhea, we have had the opportunity to evaluate the culture method in a group of proved cases of chronic gonorrhea.

In 1940, we took cultures for the gonococcus from a series of cases immediately after admission and before the institution of treatment. Only 35 per cent of these cultures were reported positive. The cultures were repeated in those reported negative on the first examination, and the positives were increased to a total of 50 per cent. In other words, two consecutive cultures were negative, in the absence of treatment, in half of our newly admitted proved cases of chronic gonorrhea. The following year a similar study was made by another bacteriologist in our Laboratory. Only 55 per cent of positive reports were obtained by repeated culture examinations (varying from two to three in number) of untreated patients.

In the spring of 1942, with the collaboration of Dr. Alfred Cohn of the Gonococcus Research Laboratory of the New York City Department of Health this subject was further investigated.

During the period from February 9 to June 1, 1942, 81 female patients with culture positive for gonorrhea were examined. Sixteen of these were excluded from the report because of (1) early release from the hospital obtained through the Director of the Social Hygiene Division, (2) treatment received prior to hospital admission, (3) lack of cooperation on the part of the particular patient.

As noted previously, all 65 patients had been found culturally positive for gonorrhea by the Gonococcus Routine Laboratory of the New York City Department of Health. When re-examined on admission to the Kingston Avenue Hospital (all specimens for this study being sent to the Research Laboratory for culture), only 39 (60 per cent) were found to have positive cultures. Since this figure includes 6 cases which were positive only on the urethral culture, only 33, or 50.7 per cent, were found positive on cervical cultures alone. Of the total of 47 positive cervical cultures obtained from these 33 patients, 10 were accompanied by positive smears, 2 by suspicious, and 35 by negative smears, which again shows cultures much more accurate than smears. Only one positive cervical smear was observed where the corresponding culture was negative. Of the 31 positive urethral cultures, 5 were accompanied by positive and 2 by suspicious smears; the remaining smears were found negative.

The interval between the first examination at the House of Detention and the first at Kingston Avenue Hospital varied from two to thirty-three days with an average of 6.8 days. The length of the interval was

not in any way correlated to the occurrence of negative cultures. There were patients who yielded negative cultures after an interval of two days and others with positive cultures after more than thirty days. This fluctuation may have been due to the variation in the length of the infection. All were cases of chronic gonorrhea, but no accurate data on the duration of the infection could be obtained. It may be assumed that the women were examined at different stages of the disease. This is one of the many factors that may explain the decrease in the number of positive findings on re-examination. Another is the fact that for obvious reasons, these patients were greatly interested in concealing their infection and probably used various antiseptic substances, such as intravaginal soap, etc., which might have influenced the positive bacteriology of the cervix.

Treatment

On our service, gonorrhea is treated by means of sulfathiazole by mouth, 60 gr. daily for seven days. No local treatment is given and no douches permitted.

A. Clinical Results

Of 58 patients who had profuse mucopurulent discharge from the cervix before sulfathiazole treatment, 25 (43 per cent) were still noted to have profuse mucopurulent discharge three weeks after the end of treatment, although 3 consecutive post-treatment cultures taken at weekly intervals had been reported negative. Twelve (20 per cent) of the 58 who had profuse mucopurulent cervical discharge before treatment had moderate mucopurulent discharge three weeks later, although 3 consecutive post-treatment cultures were negative. Thus 37 of these 58 patients (63 per cent) with profuse mucopurulent cervical discharge, although negative bacteriologically, had not become negative clinically.

Eleven patients who entered the hospital with moderate mucopurulent cervical discharge were noted to have but scant discharge three weeks after chemotherapy was terminated. Of 12 patients who had scant or no discharge before treatment, although their cultures had been positive, none had discharge three weeks later.

B. Bacteriologic Results

Apparent bacteriologic cure was achieved in 64 of the 65 patients. The remaining patient was resistant to sulfonamides and was finally cured after fever therapy.

At the onset of the study, smears and cultures were taken from the urethra and cervix every second day for a period of three weeks after termination of sulfathiazole therapy. Later this schedule was changed to six smears and cultures over a similar period. Provocatives of 1 per cent and 3 per cent zinc sulfate and 5 per cent silver nitrate were used but without any apparent success in increasing the positive findings.

The bactericidal test developed by the Gonococcus Research laboratory which determines the in vitro reaction of gonococcus strains to sulfathiazole was performed on 23 of the 39 gonococcus strains isolated from infected patients. Nineteen showed susceptible strain in vivo and vitro. The strain obtained from a clinically resistant patient showed resistance in the test tube also. There were 3 intermediate strains of patients who responded to treatment.

Trichomonas vaginalis was found in the vaginal secretion in two-thirds of our cases and remained unaffected by sulfathiazole treatment.

No statement concerning clinical cure can be made from this study, because unfortunately the time of observation after therapy was too short.

Summary

1. A single gynecologic examination just before admission to the hospital revealed clinical evidence of infection in only 30 per cent of a group of prostitutes culturally positive for the gonococcus, as compared to 85 per cent when the patients were repeatedly examined in the hospital.

2. Cultures for the gonococcus were taken before institution of treatment from 65 women with chronic gonorrhea who had had positive cultures just before admission. Only 60 per cent were found positive on repeated culture examinations, while a single culture was positive in only 45 per cent.

3. In view of our findings in untreated cases, the limitations of the culture in the diagnosis of chronic gonorrhea are obvious. A few negative cultures have limited value in ruling out the diagnosis, or as proof of cure.

4. In the clinically positive cases treated with sulfathiazole, 63 per cent still had moderate or profuse mucopurulent cervical discharge when examined three weeks later, although gonococci were no longer found on culture.

5. The greater value of the culture as compared to the smear, in chronic gonorrhea, was again demonstrated.

6. Trichomonads were found in two-thirds of our cases, and persisted in spite of sulfathiazole therapy. The presence of trichomonads should not cause us to overlook a possible gonorrhea.

THE USE OF SODIUM SULFATHIAZOLE IN THE TREATMENT OF SEPTIC ABORTIONS

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THIS study was made in an effort to accomplish two specific objectives. The first was an attempt to reduce morbidity and mortality in cases of septic abortion by the use of specific drug therapy, along with the routine that had been used prior to the advent of such a drug, and second to reduce the hospitalization period, which is of great importance in dealing with a large charity service.

We began this routine on Jan. 1, 1941, and continued it for one year. All cases admitted to our service were handled in the same manner; our controls being obtained from those admitted to the Tulane service during the year 1940. The following was our method of handling each case.

Procedure

On admission to the ward the patient was prepared for surgery and the senior resident called. This work was handled by the latter of the authors. By him or under his supervision all visible products of pregnancy were removed from the vaginal canal. No attempt was made to remove any products from the cervical canal or the uterine cavity. Pitocin, 1 c.c., was given on admission and whenever necessary for free bleeding. Ergotrate, gr. 1/320, was given every six hours for three days. Vaginal packing was used only for profuse uterine bleeding which could not be controlled by other measures. When used, the pack was always removed within twenty-four hours. When such a procedure was to be carried out, the patient was placed in the Sims or knee-chest position, and cotton balls, saturated with saline, were used, placing them against the cervix in a concentric manner.

Laboratory work included urinalysis, blood and cervical cultures, and complete blood picture. If the total red blood count was below 3,500,000, the patient was given a transfusion of from 500 to 1000 c.c. of whole blood.

The cervical and blood cultures were taken by the bacteriologic department of the hospital, and these results will be shown later.

Sodium sulfathiazole was given only to those proved to be septic, and not alone on history of chills and fever or of instrumentation. It has been our experience that many patients will have a temperature even up to 103° F. on admission; and following the administration of pitocin or the removal of products of pregnancy from the vagina, the temperature will return to normal within twenty-four hours and remain so. For that reason no patient was considered septic until the temperature had remained at 100.4° F. or higher for twenty-four to forty-eight hours. When this condition existed, she was given an initial

dose of 3 Gm. of sodium sulfathiazole by mouth and then 1 Gm. every six hours for five or more days. The drug was stopped if red blood cells appeared in the urine, if severe leucopenia developed, or if other signs of severe toxic reaction resulted.

Having adopted a conservative form of treatment in these cases, it was not our practice to perform curettement except in those cases of uterine bleeding that could not be controlled by any other means. When we found it necessary to curette, it was not done unless the patient had never been septic or had been afebrile for one week.

The routine used in obtaining and studying the cultures was obtained from the bacteriologic department of the hospital and is as follows:

For purposes of bacteriologic study two types of specimens were collected: (1) venous blood, and (2) a swab from the cervical canal. For the latter, the patient was prepared as for a sterile vaginal examination, and a sterile speculum was inserted to expose the cervix. Any clots and visible tissue were removed, and the cervix cleaned with sterile sponges. A small swab was inserted into the cervical canal to a depth of about an inch and one-half and placed immediately into a tube of glucose-brain broth.

This medium contains a piece of calf brain tissue and is additionally buffered with a small amount of crushed marble, which also provides an alkaline anaerobic environment in its immediate vicinity. It has been found to support the growth of a wide variety of organisms, including most anaerobes and the more fastidious streptococci and gram-negative bacilli.

After a preliminary incubation of three to four days, the swabs were removed and the broth subcultured to duplicate sets of infusion rabbit's blood-agar plates. One set was incubated aerobically and the other anaerobically in a phosphorus jar for four days. Occasionally smears of the broth culture revealed organisms which did not grow out on the plates, and it was found possible to maintain their viability in brain broth transplants. Distinct colony types were fished from the plates, smeared for microscopic examination, and subcultured appropriately.

Glucose-brain-broth was also inoculated with blood drawn at the same time the cervical culture was taken. Tubes containing 20 c.c. of broth were inoculated with 2 c.c. of blood. In addition, pour-plates were made with glucose-extract-agar. When growth resulted, subcultures and identifications were made in the manner described for cervical cultures. Blood cultures were observed for one month before being called negative.

Certain organisms were seen to predominate and are probably to be regarded as normal flora of the cervix. Like the streptococci of the nasopharynx and the fusospirochetes of the mouth, however, some of them are very likely capable of pathogenic activity when other conditions prepare the way. Since the flora of the cervix has not been adequately studied, to our knowledge, some remarks about the most frequently present bacteria are here appended.

Diphtheroid bacilli were not further differentiated. Organisms are so designated if morphologically and culturally they display the main characteristics of corynebacteriae.

Streptococci were named according to the type of hemolysis produced, or the lack of it. Those exhibiting large clear zones of hemolysis are designated "beta streptococcus." Those producing incomplete or green

hemolysis are called "alpha streptococcus." All others are grouped under the term "nonhemolytic streptococci," which undoubtedly includes several varieties. A markedly pleomorphic streptococcus growing aerobically or facultatively anaerobically was commonly found, for which the descriptive term "diphtheroidal streptococci" was employed.

Anaerobic gram-negative bacilli are not further differentiated in this report. Those isolated appear to belong to the group of nonsporulating obligately anaerobic gram-negative bacilli which Bergey calls "bacteriodes."

Results

TABLE I. RESULTS OF CERVICAL CULTURES IN CLEAN CASES

ORGANISM	ANAEROBIC	AEROBIC
Beta streptococcus	2	1
Alpha streptococcus	3	2
Gram-negative bacilli	38	–
Nonhemolytic streptococcus	76	77
Alcaligenes faecalis	–	2
Diphtheroid	–	49
Diphtheroid streptococcus		
Escherichia coli	–	13
Staphylococcus aureus	–	2
Staphylococcus albus	–	32

TABLE II. RESULTS OF CERVICAL CULTURES IN SEPTIC CASES

ORGANISM	ANAEROBIC	AEROBIC
Beta streptococcus		
Alpha streptococcus	2	1
Gram-negative bacilli	10	–
Diphtheroid	–	11
Diphtheroid streptococcus	–	3
Escherichia coli	–	–
Staphylococcus aureus	–	2
Staphylococcus albus	–	4
Nonhemolytic streptococcus	12	17

There were a total of 124 clean cases that had a positive cervical culture; this representing 78 per cent of the clean cases reported. In the septic cases there were 34 positive cervical cultures, which is 77 per cent of the total number reported. It thus appears that the true present condition and prognosis of the patient could not be ascertained by a knowledge of the cervical culture alone.

TABLE III. RESULTS OF CASES STUDIED

Total number of cases	200
Total clean cases	156 (78%)
Total septic cases	44 (22%)
Total curettements	6 (3%)
Total vaginal packs	3 (1.5%)
Total number of deaths	2 (1%)

As shown in Table III, there were a total of 200 cases studied. Of these, 156 (78 per cent) were clean cases, and 44 (22 per cent) were septic. There were only 6 cases where curettement was found necessary, as compared to a study made in 1940 which revealed the fact that

in 172 cases of abortion, curettement was done in 24 (13.9 per cent). These were handled, however, by separate members of the staff before a definite routine was established, and might explain the great difference between the two years. However, this number of curettements is not excessive, even where one is following a conservative form of treatment.

The two deaths that occurred were both cases of criminal abortion. The first was that of a patient who was admitted to the hospital in a moribund state and died within twenty-four hours without receiving any specific drug therapy. The second death occurred in a patient who was admitted with generalized peritonitis and severe toxic jaundice. She responded temporarily to sodium sulfathiazole therapy, but died rather suddenly of pneumonia seven days after admission.

TABLE IV. RESULTS IN CLEAN CASES

Average hospital stay	5.4 days
Number of curettements	5 (3.1%)
Number of vaginal packs	2 (1.2%)
Number of cases transfused	28 (17%)
Number of cases admitted to be criminal	11 (7.1%)

The average hospital stay to our knowledge compares favorably to that found in other reports. The small number of patients who were packed is of interest, and in our opinion is what it should be.

TABLE V. RESULTS IN SEPTIC CASES

Average hospital stay	10.1 days
Number of curettements	1 (2.2%)
Number of vaginal packs	1 (2.2%)
Number transfused	20 (45.4%)
Number of cases admitted to be criminal	12 (27.2%)

As shown in Table V, the average hospital stay of septic cases that received sodium sulfathiazole was ten days. In studying a similar number of septic patients who were admitted to the Tulane service during the year 1940, and who did not receive any specific drug therapy, we found that the average hospital stay was thirteen days. Among those patients who received specific therapy, the average duration for the reduction of temperature to normal was accomplished in approximately three days.

The one curettement shown in Table V was performed on a patient who returned to the hospital after completion of her septic course because of recurrence of uterine bleeding. Being afebrile she was curetted and her postoperative course was uneventful.

One vaginal packing was done in this series, because of uncontrollable bleeding in a patient whose red blood count had dropped to 1,200,000.

TABLE VI. AMOUNTS OF DRUG USED

Average amount of sodium sulfathiazole used	24.4	Gm.
Largest amount of sodium sulfathiazole used	72	Gm.
Smallest amount of sodium sulfathiazole used	6	Gm.

TABLE VII.   TOXIC REACTIONS

Severe nausea	4 Cases
Severe vomiting	1 Case
Severe headache	1 Case
Leucopenia	1 Case

As will be noted in Table VI, the average amount of sodium sulfa-thiazole used required five days, following the routine which we adopted. The toxic reactions were relatively uncommon and in only one instance was it necessary to discontinue the use of the drug; this being the patient that developed leucopenia.

TABLE VIII.   COMPLICATIONS

Cystitis	1 Case
Cul-de-sac abscess	1 Case
Pyelonephritis	1 Case
Infectious arthritis	1 Case
Generalized peritonitis	2 Cases

The complications occurring in this series are shown in Table VIII. Uneventful recovery was made in all instances, except that of the two cases of generalized peritonitis, these having been discussed in detail previously.

TABLE IX.   MORTALITY OF ABORTIONS.   CHARITY HOSPITAL 1937 TO 1941

YEAR	ENTIRE HOSPITAL	TULANE	DEATHS ENTIRE HOSPITAL	TULANE DEATHS
1937	1,325	491	22, 1.6%	7, 1.4%
1938	987	392	13, 1.3%	3, 0.7%
1939	927	346	13, 1.4%	4, 1.1%
1940	1,140	419	10, 0.8%	5, 1.1%
1941	957	369	5, 0.5%	2, 0.5%

Table IX shows that the mortality during the past five years has shown a steady downward trend; both for the entire hospital and our own service.   The lowest figures for both occurred during the years 1940 and 1941, and we are of the opinion that this has been accomplished through the use of specific chemotherapy.

Summary and Conclusions

We have presented a definite conservative routine for the handling of abortions, with the addition of specific drug therapy in septic cases. By following this routine we have shown that the morbidity, mortality, and length of hospital stay have been greatly reduced.   We have also reduced the number of curettements to a minimum.

Cervical cultures were found to be of little value in determining the presence of pelvic sepsis, as an equal number of positive cultures were obtained in the clean cases.

Sodium sulfathiazole therapy gave good results in all cases, irrespec-tive of type organism found.

210 BAUONNE STREET

VINBARBITAL SODIUM FOR OBSTETRIC AMNESIA AND ANALGESIA

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BECAUSE of the lack of uniformity in the various methods of obtaining obstetric amnesia and analgesia and also the controversy concerning them, this study was conducted to determine a logical routine in alleviating the discomfort and side-effects of parturient women and in providing maximum safety for the newborn.

The excitation which we had experienced in our obstetric service with sodium ethyl (1-methylbutyl) barbiturate and the lack of cooperation with sodium allyl (1-methylbutyl) barbiturate, led to a further search among the barbiturates for a more satisfactory agent. Sodium ethyl (1-methylbutyl) barbiturate, in an initial dose of 6 to $7\frac{1}{2}$ gr., produced a large percentage of cases exhibiting excitement during the first stage of labor; undesirable aftereffects, such as a "hangover," were also frequently experienced. A 3 gr. initial dose of sodium allyl (1-methylbutyl) barbiturate was found to be insufficient in the majority of cases to give a therapeutic response and, although the initial dose was increased, a uniform response was lacking.

Among the more recent developments in the barbiturate field were the delta-1-alkynyl groups of which "Delvinal" sodium vinbarbital* has been made available for general clinical use. The favorable reports in the literature[1-5] concerning the pharmacologic and clinical investigation of this barbiturate led us to investigate its value as an aid in producing satisfactory obstetric amnesia and analgesia.

Cognizant of the occasional untoward effects of the barbiturates, both immediate and delayed, we endeavored to individualize the dose when administering this drug, adapting the dosage to the patient, rather than the patient to a standard dose. At no time did we feel that it was advantageous to give so large a dose that marked depression might occur.

"Delvinal" sodium vinbarbital, a more soluble barbiturate, is classed as a sedative, hypnotic, and analgesic. Its principal site of action is in the diencephalon. It is rapidly absorbed when administered orally and its action is of short duration. The greater portion of the drug is detoxified in the liver.

*Delvinal vinbarbital sodium is the nonproprietary name for sodium 5-ethyl 5-(1-methyl-1-butenyl) barbiturate. It is prepared by Sharpe & Dohme, Philadelphia, Pa.

Material

This study was conducted at the Jefferson Medical College Hospital on 117 unselected women in labor. These patients were grouped as follows:

Primiparas	92	78.6%
Multiparas	25	21.4%

This corresponds to our ratio of ward admissions in primiparas and multiparas. We felt that we were fortunate in having so large a percentage of primiparous patients, since it is in this group that analgesia and amnesia play their greatest roles.

The youngest patient in our series was 14 years of age and the oldest was 45 years. The individual ages ranged as follows:

AGE	NUMBER OF CASES
14	1
15-20	60
21-25	35
26-30	12
31-35	3
36-40	5
41-45	1

Approximately 92.3 per cent of our patients were under 31 years of age.

Presentation was as follows: 113 cephalic and 6 breech. According to position they were as follows:

L.O.A.	64
R.O.A.	42
L.O.P.	2
R.O.P.	5
Breech	6

Mention should be made concerning some of the complications that have been observed in this group. There was one case of polyhydramnios, one of syphilis, and one of placenta previa of the marginal type.

Administration of the Drug

When this study was undertaken, we were concerned with determining the proper dose, that is, one that would give proper analgesia and amnesia with minimal deleterious effects on the mother and the child. Starting with small doses, the drugs was administered in increasing amounts until the desired therapeutic effect was obtained. This dose was found to fall between 3 and 6 gr., and, after careful evaluation, we determined that the average initial dose of sodium vinbarbital was 4½ gr. As previously mentioned, the dose was adjusted to the patient, and, therefore, some patients received an initial dose of 3 gr. while others required 6 gr. This drug was given and supplemented with scopolamine in most cases.

The initial dose of 4½ gr. of sodium vinbarbital was administered early in the first stage of labor, either when contractions became defi-

nitely rhythmical in character or when the cervix showed a 2 cm. dilatation. One-half hour later, when the sedative action was manifest, $\frac{1}{150}$ gr. or $\frac{1}{200}$ gr. of scopolamine was administered hypodermically. This procedure was found to definitely reduce the possibility of excitement during the first stage of labor. Additional doses of sodium vinbarbital were given dependent upon the response of the patient to the initial dose. One and one-half to 3 gr. were administered at one- to four-hour intervals as required to maintain the patient in a zone of effective amnesia and analgesia. Some individuals required $1\frac{1}{2}$ gr. repeated several times; others required 3 gr. less often. The largest total dosage of sodium vinbarbital administered to a single patient in labor was $13\frac{1}{2}$ gr., without any untoward effects to the mother or child. Our average total dose administered was $6\frac{2}{3}$ gr. In several patients the scopolamine was repeated in decreasing doses, such as $\frac{1}{200}$ and $\frac{1}{400}$ gr.

Duration of Labor

The duration of labor was under twelve hours in 54 patients (46.1 per cent), and it was less than twenty-four hours in 87 patients (74.3 per cent). Considering the number of primiparous patients, the duration of labor compares favorably with the average duration of labor.

Method of Delivery

Spontaneous	99 (including 3 spontaneous breech deliveries)
Forceps	17
Breech extractions	3
Episiotomy	43

The number of spontaneous deliveries is evidence that the analgesia and amnesia obtained by the use of sodium vinbarbital did not increase the number of operative deliveries.

Supplemental Anesthesia

Supplemental anesthesia, as indicated in the following table, was administered to 83 patients, or 71.8 per cent, during the second stage of labor.

	PATIENTS
N_2O—O_2	15
N_2O—O_2 (induction) and ether	63
Ether	5
No anesthesia	34

Effects on Mother

It is of considerable importance to evaluate the effect of an analgesic agent on the contractility of the uterus following the birth of the child, and especially after the separation of the placenta and following its expression. In our series we encountered only one case of bleeding that was of considerable magnitude. This occurred in a patient whose pregnancy was complicated by a marginal placenta previa. There was no indication that the use of "Delvinal" sodium vinbarbital increased post-partum hemorrhage.

Effects on Babies

There were delivered from this group of patients (117 mothers) 119 babies (two sets of twins). Of these, 118 were born alive. There was one stillborn macerated fetus (Wassermann negative). This child was dead before the onset of labor.

The color of the babies born alive was as follows:

Good	98
Fair	18
Poor	2

It was felt that determination of the onset of breathing in these infants was of considerable importance. Therefore, we are listing the time at which the respiratory effort was established: Immediate, 101; slightly delayed, 17; delayed, –. 85.6 per cent of the babies breathed as soon as born. At no time was there any great difficulty encountered in the establishment of respiration in the babies born of this entire group of mothers.

When administering an analgesic agent, a consideration very often ignored or overlooked is the effect it might exert on the conduct and cooperation of that particular patient both during labor and the immediate post-partum period. These side-effects are not only embarrassing, but difficult, and sometimes even dangerous. We have found that our patients responded in about 85 per cent of cases to moderate doses of sodium vinbarbital (3 to 6 gr.) followed one-half hour later by $\frac{1}{150}$ gr. of scopolamine. As previously noted, we individualized the routine administration, and, therefore, some received subsequent doses. One patient received $13\frac{1}{2}$ gr. Yet our patients were not unruly, nor did they need special restraining apparatus. They slept or rested between pains, and in some there was evidenced slight moaning when a uterine contraction occurred. When it became necessary to examine these patients, they responded to orders and were cooperative. It should be mentioned that any patient who receives an analgesic agent should not be left alone, no matter how ideal and apparently foolproof it may be.

When the patient was returned to her bed, following the delivery of the baby and expulsion of the placenta, there was little evidence of the so-called "hangover" that is annoying to the physician and the family of the patient. A large percentage of the patients had several hours' normal sleep following delivery which we feel is of definite value in aiding restorative powers. We feel that this was accounted for by the solubility, lack of toxicity, and rapid elimination of the drug.

Summary of Results

In this series, 117 pregnant women received sodium vinbarbital in the first stage of labor as an agent to produce amnesia and analgesia. Our average, or initial dose, was $4\frac{1}{2}$ gr. followed in one-half hour by $\frac{1}{150}$ gr. of scopolamine. The analgesia was augmented by subsequent doses of the barbiturate in doses of $1\frac{1}{2}$ to 3 gr., which were administered when there was a further need for analgesia. The largest single dose of sodium vinbarbital administered to one patient was $13\frac{1}{2}$ gr. The average total dose was $6\frac{2}{3}$ gr.

There were 92, or 78.6 per cent, primiparous patients, and 25 or 21.4 per cent, multiparas. The youngest patient was 14 years of age, and the oldest 45 years of age. Approximately 92.3 per cent were under 31 years of age.

In this group, 83, or 71.8 per cent, of the patients received supplemental inhalation anesthesia at the time of delivery.

Length of labor: 54, or 46.1 per cent, were in labor less than twelve hours; 87, or 74.3 per cent, were in labor less than twenty-four hours.

Method of delivery: 99 (including 3 breech presentations) were delivered spontaneously. Forceps were used in 17 cases and there were 3 breech extractions.

Of the babies, 118 were born alive, and there was one stillborn macerated fetus, an intrauterine fetal death.

Of the children born alive, 101 breathed and cried immediately. In 17 there was slight delay; at no time was any great difficulty encountered in obtaining respiratory response.

Conclusion

1. It was found that "Delvinal" sodium vinbarbital was a rapidly absorbed and quickly eliminated barbiturate. In doses mentioned in this paper, it was without harmful effects as far as the mother and child were concerned, although good amnesia and analgesia were obtained in 85.5 per cent of the cases.

2. We feel that this drug should be used in the first stage of labor and supplemented by inhalation anesthesia during the second stage.

3. This drug may be used in patients at different ages, as proved in our group, which varied from fourteen to forty-five years of age. Complications of pregnancy do not contraindicate its use, since it was used in cases of polyhydraminos, syphilis, and placenta previa.

4. Labor was not prolonged by its use, as 46.1 per cent of our patients had labors of less than twelve hours, and 74.3 per cent had labors of less than twenty-four hours, and 99 patients delivered spontaneously.

5. "Delvinal" sodium vinbarbital apparently does not exert untoward effects as far as post-partum bleeding is concerned, since there was only one case of post-partum hemorrhage that occurred in a case of marginal placenta previa.

6. To the 117 mothers there were born 119 children, of which 118 were alive, and one was a stillborn macerated fetus occurring in a case of intrauterine fetal death.

7. There was little difficulty in the inauguration of respiration.

8. We feel that this drug does not exert a depressing effect on the offspring.

9. Patients with good analgesia and amnesia did not become unruly or uncooperative. When general anesthesia was given, it was taken very smoothly, and when the patient was returned to her room there

was absence of restlessness and the so-called "hangover," which is ascribed to many other barbiturates.

References

1. Hendrix, J. P.: J. Pharmacol. & Exper. Therap. **68:** 22, 1940.
2. Davidoff, E.: Dis. Nerv. System **2:** 288, 1941.
   Idem: Psychiatric Quart. **15:** 370, 1941.
   Davidoff, E., and Goodstone, G. L.: M. Rec. **155:** 22, 1942.
3. Marvin, F. W.: Anesth. & Analg. **21:** 229, 1942.
4. Borthwick-Leslie, K.: Canad. M. A. J. **46:** 345, 1942.
5. Hendrix, J. P.: Am. J. M. Sc. **204:** 93, 1942.

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TESTICULAR TUBULAR ADENOMA IN TWO SISTERS*

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THE extreme rarity of hereditary testicular tubular adenoma and its significance in relation to problems of hermaphroditism and intersexuality appear to justify the publication of the two following cases.

CASE 1.—The patient, a 27-year-old married woman, complained for four months of various insignificant disorders, which according to her opinion were due to excessive smoking. On examination a pelvic tumor was found and an operation advised. The patient never had menstruated, but otherwise was without gynecologic complaints. Sexual intercourse was normal and satisfactory. Her libido was strong and exclusively directed toward the male sex.

Examination.—The stature of the patient, her features, proportions, her hair growth, and the development of her breasts were typically female. There was, however, complete absence of axillary hair and almost complete lack of pubic hair.

Except for a moderate hypoplasia of the major and minor labia, the external genitals were normal. The vagina was of normal length and width and ended blindly. Neither the cervix nor the uterus was palpable. An apple-sized, hard, nodular, movable tumor, however, was palpable in the left lower quadrant, apparently representing the left gonad. The right gonad was not found on examination. The size and shape of the pelvis were normal and of female type.

Operation.—(December 31, 1923.) The abdomen was opened through a low transverse incision. On the left side a mass was found where the left gonad is ordinarily located. It consisted of a whitish, freely movable tumor of about three inches in diameter. On the right side, a similar mass occupying a somewhat higher position was seen. It was ovoid in shape, had a smooth surface and contained two pea-sized palpable nodules. Both gonads were connected by a transverse, arched peritoneal fold extending between bladder and rectum and apparently representing a Muellerian rudiment. Each lateral portion of this peritoneal reduplication contained a nodule about 1 cm. in length and thickness.

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*The patients were operated upon in Vienna. The blocks of the pathologic material were cut in the laboratory of Mt. Sinai Hospital and the slides studied under the supervision of Dr. Paul Klemperer, pathologist to the Hospital.

On the top of the right nodule there was a small formation which could be recognized easily as a tubal ampulla. Both gonads were removed, the right one together with the adjacent nodule. In addition an appendectomy was performed.

The postoperative convalescence was uneventful. But several weeks after the operation the patient started to suffer from frequent and severe flushes which gradually diminished and disappeared after several years. She was observed for thirteen years after the operation. Her weight increased only slightly and her sexual reactions remained normal.

CASE 2.—Several months after the operation of the first patient I was consulted by her younger sister. She was 26 years old, married, but had never menstruated. Contrary to her sister she had always been frigid and without sexual desires. Having grown rapidly in her childhood, she was the tallest in her class for some time. But after the thirteenth year her growth became very slow and soon stopped completely. Likewise her breasts developed prematurely and remained stationary after the age of nine. Her past medical history included scarlet fever, typhoid, and bilateral hernioplasty.

Examination.—The patient was 4 feet 7½ inches tall, slightly corpulent (115½ pounds) and strikingly muscular. Her legs were short and slightly curved. The body length was 2 feet 1 inch above the symphysis and 2 feet 6½ inches below. By her short, vigorous stature she resembled a chondrodystrophic individual, but did not show the other typical characteristics of chondrodystrophy. Her features and hair on the head were of female type. The breasts were well shaped, their size corresponding to those of a girl of about sixteen. The axillary hair was absent, the pubic hair was indicated only slightly.

The external genitals were markedly hypoplastic, the mons veneris poor in fat, the labia majora underdeveloped, thin, and flat. The labia minora formed stunted, low projections elevated over the surroundings only in the region of the clitoris. The vagina was 6 cm. in length and ended blindly. Neither cervix nor uterus could be detected. In the cul-de-sac, two ovoid-shaped, nontender tumors were palpable, the left one 3½ by 2½ by 2½ inches, the right one a little smaller.

Operation.—(September 15, 1924.) A laparotomy was performed through a lower midline incision. Adhesions between omentum and the right inner inguinal ring derived from the former hernioplasty were dissected. Both gonads were found changed into partly solid, partly cystic tumors, the left one being 3½ by 2½ by 2½ inches, the right one somewhat smaller. Both tumors were densely adherent to their surroundings. Each gonad was connected by a thick ligament to an archlike peritoneal fold extending transversely between the bladder and rectum, and representing the rudimentary Muellerian ducts. The fold was thin in its central portion, but became thicker laterally, finally forming muscular nodules from which short round ligaments projected into the inguinal canals. Between the right ovarian ligament and the rudimentary uterus, a small rudimentary tube was demonstrable. Both tumors were freed from adhesions and removed.

The convalescence was uneventful. However some weeks after the operation the patient began to complain of unusually severe flushes and sweats, occasionally also of numbness of the hands. These disorders were continuous and responded only slightly to treatment. The flushes continued for thirteen years and have had to be treated continuously by various estrogenic preparations.

The occurrence of such striking sexual abnormalities in two sisters suggested the investigation of their heredity. With the help of the two patients, their mother, a grandmother, an aunt, and a physician-relative, valuable information was obtained which enabled me to set up a genealogic tree of their kin. This showed that there were several other members among the kindred who were affected with marked sexual abnormalities, the hereditary taint apparently transmitted from grandmother to her children and grandchildren. There was a preponderance of descendants with feminine appearance.

Pathologic Findings.—The left gonad of the first case was composed of a smaller dark-brown portion and a much larger yellowish, nodular predominantly solid, partly cystic mass. The right gonad showed the same dark-brown color on cross section as the small portion of the left
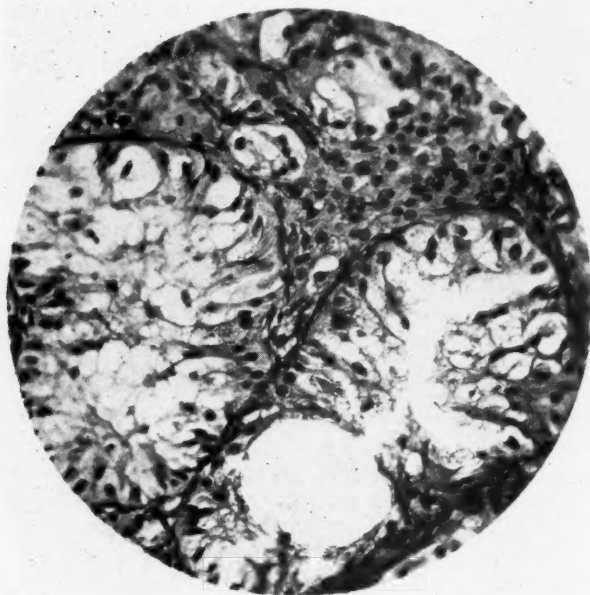
Fig. 1.—(Case 1.)   Section of left gonad, area with canaliculi lined by Sertoli cells. Numerous interstitial cells.   ($\times 260$.)

one. The yellowish mass predominant on the left gonad was restricted here to two pea-sized nodules.

In the second case both gonads consisted exclusively of a yellowish tissue which, contrary to the first, was solid only in small areas and riddled by numerous cystic cavities varying in size and filled with colorless fluid.

The microscopic examination proved the brown portion to consist of underdeveloped, but easily recognizable, testicular tissue with typical canaliculi and numerous Leydig cells (Fig. 1). Here and there the interstitial cells were massed in well-defined, dark-stained nodules, resembling the well-known interstitial cell-hyperplasia repeatedly found in cryptorchic testicles.

As a rule, the canaliculi were separated by ordinary loose connective tissue. But here and there small areas of characteristic spindle-shaped

ovarian stroma cells were discernible representing the only demonstrable
trace of ovarian tissue (Fig. 2). In spite of a thorough search, neither
ova nor follicles could be found.

The yellowish tumor had a different structure (Fig. 3). It consisted
of straight or curved ramified cords or canaliculi, lined by a single row
of fairly regular high cylindrical, palisade-like epithelial cells. Areas
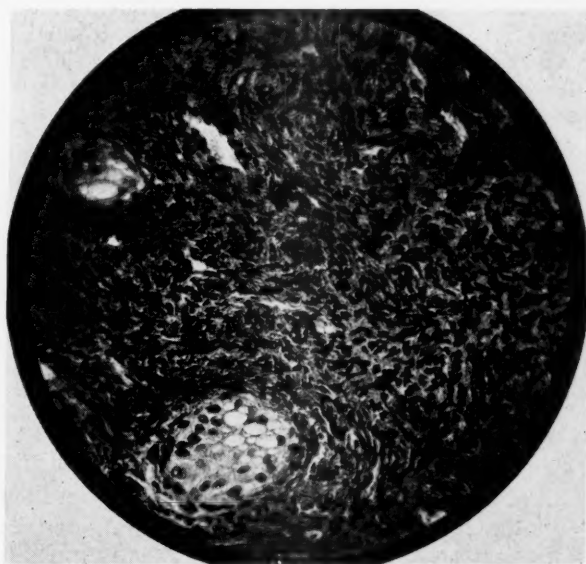of closely aggregated canaliculi were separated by strands of coarse,

Fig. 2.—(Case 1.)   Section of left gonad, ovarian stroma including epithelial cords
with vacuolated cells.   (×200.)
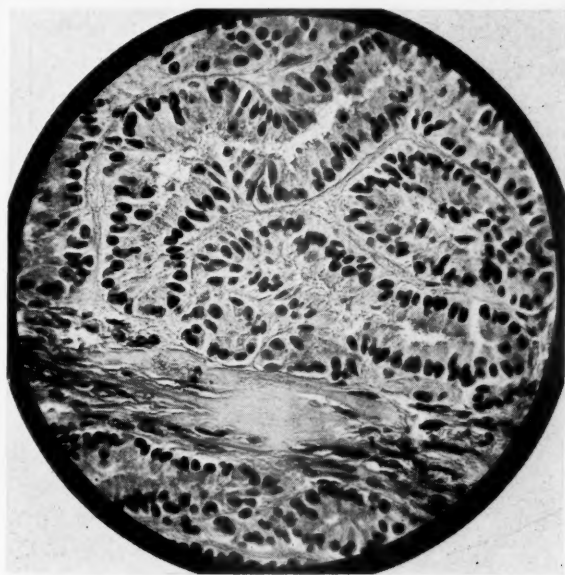
Fig. 3.—(Case 1.)   Left gonad, tumor tissue.   (×260.)

often hyalinized or even calcified connective tissue. There were neither Leydig cells nor ovarian stroma cells present within this yellowish tumor. Transitional stages between the typical testicular canaliculi and the canaliculi of the tumor showed the close relationship of the two structures.

The gonads of the second case consisted almost exclusively of the same adenomatous tissue. Only few tubules resembled typical underdeveloped seminiferous canaliculi. Most of the interstitial tissue consisted of ordinary connective tissue with a great tendency toward hyalinization and calcification. Only here and there small areas of closely aggregated spindle cells resembling ovarian stroma were interspersed between the canaliculi.

Discussion

Two patients are described in whose family there were other members with abnormalities of their sexual organs and their secondary characteristics. Though both individuals had a normal female exterior and feminine sexuality, and most parts of their sexual organs were female, their gonads had predominantly male characteristics. They harbored a tumor which undoubtedly, because of its structure and its connection with testicular canaliculi, has to be designated as a testicular tubular adenoma. While the gonads of the second case were almost completely composed of this tumor, the gonads of the first case contained large areas of real testicular tissue with under-developed canaliculi and abundant Leydig cells. On the other hand, scattered areas of ovarian spindle cell stroma prove that the gonads did not consist entirely of male tissue.

Though neither ova nor follicles were found in the gonads the presence of ovarian stroma on the one hand, and the presence of testicular tissue on the other hand, mark the gonads as ovotestes with a great predominance of the male portion. This assumption does not seem to be forced, since in the reported cases of ovo-testis, with or without a tubular adenoma, all possible transitions from functioning ovarian tissue to insignificant ovarian traces, have been met. In any destructive process, the ovarian stroma represents the most resistant part of the ovary and remains as the last residue of the female gonad.

It seems safe to assume that these misshapen gonads were not functionless in these two cases, as their removal was followed by unusually severe and longlasting deficiency symptoms. It is very improbable that the loss of the small remnants of ovarian tissue was responsible for the severe postoperative flushes and sweats in our two cases. One would rather have to attribute these disturbances to the loss of the highly predominant male tissue. Similar disorders were noticed by R. Cadiz and A. Lipschuetz,[1] Wagner,[7] and Klaus,[4] after the removal of testicles in otherwise female individuals. Since such intensive vasomotor and secretory upsets are not seen in males after the removal of testicles, one must

assume that the effect of gonadic deficiency depends primarily on the specific reactivity of the female organism.

The testicular tubular adenoma is a very rare tumor. It is impossible to evaluate the exact number of such cases since description and illustration in some case reports do not allow a strict differentiation from other closely related tumors. The occurrence of a testicular tubular adenoma in two sisters is unique.

The testicular tubular adenoma represents the most differentiated and most typical form of a group of neoplasms, which, according to R. Meyer, are derived from a male anlage and therefore are called arrhenoblastomas. Its resemblance to normal testicular tissue is evident. Notwithstanding that fact, such adenomas masculinize their hosts only in exceptional cases. As a rule, the more atypical the structure of the arrhenoblastoma the more masculinizing is its effect. A priori, one would expect the contrary. Heretofore, all efforts to explain this puzzle have failed.

To understand the origin of testicular adenomas a short embryologic review of gonadal development is necessary. In the first stages of development, the gonads of both sexes have the same structure. In embryos of 9 mm. length, radiating cords of epithelioid cells suddenly occur below the germinal epithelium of the genital fold, forming the so-called primary germinal cords. At a later stage, secondary germinal cords appear under the germinal epithelium, pushing the primary cords deeper toward the center of the gonad (Gruenwald[3] and others). There the primary cords join an epithelial network, the so-called rete, which also originates within the gonadal blastoma and which, by means of the urogenital junction, meets the neighboring tubules of the primitive kidney, the Wolffian body.

Qualitative and quantitative changes of the primary and secondary germinal cords mark the sex of the gonad. Generally one can say that in the testicle the primary and in the ovary the secondary cords predominate in quantity and importance. In the male gonad all the single constituents of the indifferent gonad grow and develop in the direction of the original architectural plan. The prevailing part of the seminiferous canaliculi originates from the primary germinal cords. In contrast, in the female gonad only the secondary germinal cords build up the essential ovarian tissue. The primary germinal cords, the rete and the urogenital junction regress under normal conditions, forming only insignificant rudiments in the ovarian hilum.

These rudiments represent the potential male part of the ovary. From the embryologic standpoint every ovary represents an incomplete ovotestis or, stressing the sterility of the central male part, a testoid according to A. Kohn.[5] Under pathologic conditions the male rudiments may awake to new life and give origin to tumors with male character.

The medullary cords, i.e., the residues of the primary germinal cords, may further develop and form testicular tubules and various kinds of arrhenoblastoma.

According to Moszkowicz,[6] the causes of this change from female to male and the growth of a tumor on the male portion of the gonad can be satisfactorily explained by Goldschmidt's intersexuality theory. All the cells of the organism are bisexual and contain male and female hereditary factors (MMFF = ♀, MMF = ♂). It depends only on the valence of the male and female hereditary factors, whether the individual's appearance is male or female. The greater the epistasy* is, i.e., the preponderance of one type of sex determining factors over the other, the better and more marked are the characteristics of that sex and the stronger will be its resistance to all opposing tendencies.

If the epistasy is low, the first dominating sex type gradually is exhausted and at a certain moment, the "turning point," the previously suppressed sex gains predominance. The lower the epistasy is, the earlier and the more thorough is the sex inversion. If it is very early and very thorough, a genetically female individual may develop a perfect male appearance and vice versa. If the sex reversal occurs at a later stage it can transform only that part which has not yet been definitely determined. An individual whose development has started as one sex, but from a certain moment, the turning point, changes to the opposite sex, is intersexual according to Goldschmidt.[2]

There is also no doubt that the two reported cases are intersexes with the turning point occurring in the stage when the somatic characters were already definitely sex-determined, while the stage of development of the gonads still allowed them a change from female to male.

Summary

1. Two cases of benign testicular tubular adenoma in two sisters are reported. The gonads consisted preponderantly of testicular tissue; the ovarian tissue was represented only by islands of ovarian stroma. In spite of the predominantly male character of the gonads, the patients looked and felt perfectly feminine. Each sister had female external genitals, a vagina, but no or almost no uterus and only a tiny tubal rudiment.

2. The removal of the malformed gonads caused severe deficiency symptoms.

3. The genealogic tree of these sisters showed that several members had abnormalities of their sexual organs and their sexual personality which marked them as intersexual individuals.

4. The gonads of these cases are interpreted as ovotestes. Embryologic facts as well as Goldschmidt's intersexuality theory are applied to explain the origin of this malformation.

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*In Mendelian heredity the hiding of one character by another superimposed upon it, the two not being allelomorphs (Stedman).

References

1. Cadiz, R., and Lipschuetz, A.:   Arch. f. Gynäk. **153:** 593, 1933.
2. Goldschmidt, R.:   Die sexuellen Zwischenstufen.   Monographien aus dem Gesamtgebiet der Physiologie der Pflanzen und der Tiere, **23:** Berlin, 1931, Julius Springer.
   Idem: The Mechanism and Physiology of Sex Determination, London, 1923, Methuen & Co., Ltd. **8, 1:** pp. 1-259.
3. Gruenwald, P.:   Ztschr. f. Anat. u. Entwcklngsgesch. **103:** 259, 1934.
4. Klaus, K.:   Českoslov. gynaek. **15:** 67, 1936.
5. Kohn, A.:   Arch. f. Entwcklngsmechn. d. Organ. **47:** 95, 1920.
6. Moszkowicz, L.:   Ergebn. d. allg. Path. u. path. Anat. **31:** 236, 1936.
7. Wagner, G. A.:   Zentralbl. f. Gynäk. **51, 2:** 1304, 1927.

HYPERPLASIA AND LUTEINIZATION OF OVARIAN STROMA ASSOCIATED WITH MASCULINIZATION

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IT IS our purpose in this communication to present two case reports exhibiting obesity, hirsutism, and amenorrhea associated with unique ovarian alterations.   One of these patients suffered also from hypertension.   Both cases appear similar to those recently published by Geist and Gaines,[1] who apparently were the first to emphasize unusual changes observed in the ovaries.   These consisted in enlargement of both ovaries, hyperplasia of stroma cells, the presence of nests of clear cells throughout the stroma, and hyperplasia and luteinization of the theca layer of atretic follicles.   The authors generously credit Bergstrand[2] as describing in a case exhibiting Cushing's syndrome somewhat similar findings in an ovary.   In reviewing this case for ourselves we noted that Bergstrand observed perifollicular luteinization, but did not mention diffuse hyperplasia of stroma cells.   Masses of fat-staining cells are described but these he was unable to differentiate from atretic corpora lutea.   In contrast, the islands of clear cells presented no such problem to the first two authors.

Case Reports

Case 1.—The patient. M. M., a 38-year-old white woman, entered St. Vincent's Hospital April 15, 1940, complaining of severe headache, obesity, and hirsutism.   The headache, which was the most disturbing symptom, was continuous and had been present for more than ten years. At the age of 20 her weight was 90 pounds, at 30, 155 pounds, and at 38, 257 pounds.   Hirsutism had been present many years and required daily shaving and often twice a day.   Although married twenty years she had never become pregnant.   She menstruated three times in all her life, the last time in 1925.   Off and on she received courses of thyroid, pituitary, and ovarian endocrine therapy without effect.

Physical examination disclosed an extremely obese white female, weighing 257 pounds.   There was pronounced hirsutism of the face. There was no increase in hair elsewhere.   There was no hypertrophy

of the clitoris, abnormalities of the breast, or other external male characteristics. The character of the voice was female. Blood pressure was 170/110.

On April 17, under gas-oxygen-ether anesthesia an operation was performed in which both tubes and ovaries were removed. In place of the left ovary an immense multilocular cystic tumor was found filling the entire pelvic and abdominal cavities. The right ovary lay prolapsed in the cul-de-sac, buried by adhesions. Following the operation there was complete abolition of headache. There was no other immediate change. Following discharge from the hospital, the patient was seen in November, 1940. She was still obese. Hirsutism was still present and as far as could be seen appeared no different than previous to operation; this, despite the fact that the patient claimed she shaved only twice a week. In January, 1941, hypertension was found to persist, being 180/110. There was no loss of weight. Aug. 11, 1942, her weight was 253 pounds, blood pressure 160/110. There was no recurrence of headaches. The only other striking change was in her demeanor. She was cheerful and had no complaints while previous to operation she had had suicidal intents.
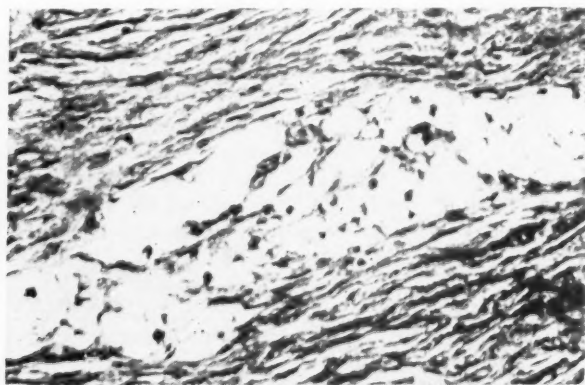
Fig. 1.—Hematoxylin and eosin section showing islands of (ovary of Case 1) clear cells surrounded by stroma cells.

Gross Pathologic Findings.—The specimen consisted of a large ovarian cyst with an attached Fallopian tube and a smaller solid ovary with attached tube. Both tubes except for distortion were essentially normal. The right ovary was elastic in consistency, enlarged, weighing 21 Gm. and measuring 5 by 3½ by 2½ cm. The outer surface contained thin fibrous adhesions. On section the ovary was solid, being composed in the main of gray colored tissue intermingled with areas light yellow in color. Numerous small cysts were present close to the surface. The ovarian cyst was large, multilocular, partially collapsed and, though much of its content had been lost, weighed 780 Gm. The walls of the various cysts were thin with smooth inner surfaces. The contained fluid was thin and straw colored. Nowhere was the tumor solid. The smallest locule measured 2½ cm. in diameter.

Microscopic Findings.—The ovarian cyst appeared to be of the pseudomucinous type with here and there small nests of clear polyhedral cells similar to those found in the Brenner tumor. The right ovary was composed chiefly of stroma cells, normal in size and appearance, ar-

ranged in interlacing bundles and whorls. Scattered throughout the stroma were many nests of clear cells (Fig. 1), from 3 to as many as 50 to a cluster. The cells were moderately large, having a thin faintly staining boundary. Cytoplasm was scant and composed of a few fine granules. Its content consisted largely of lipoid material staining
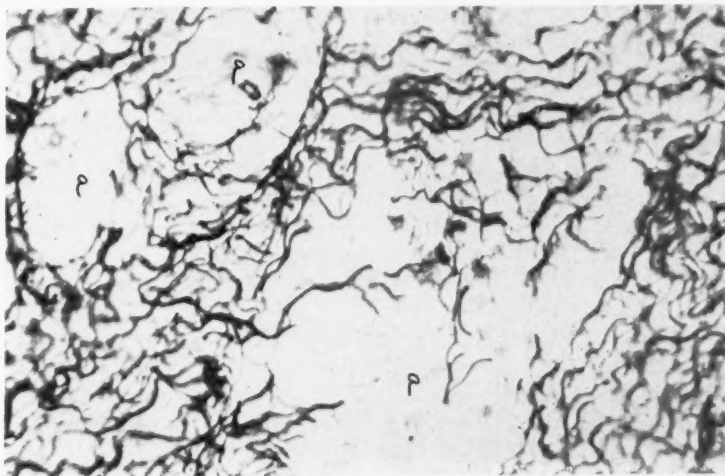

Fig. 2.—Reticulum stain, note reticulum surrounding islands (ovary of Case 1) of clear cells (*a*). Elsewhere the reticulum fibers envelop individual stroma cells.
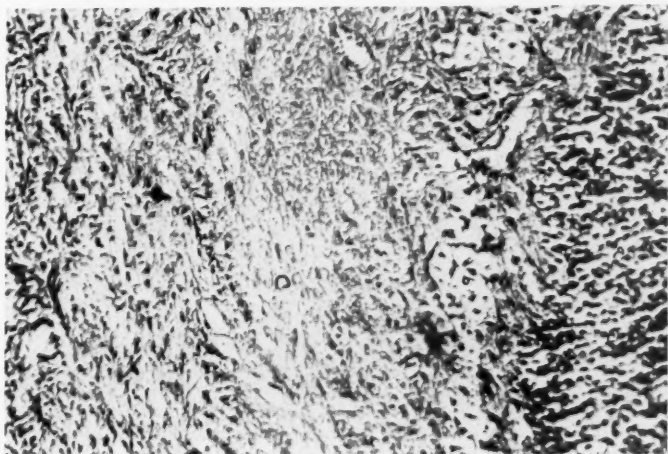

Fig. 3.—Hematoxylin and eosin section. Photomicrograph of (ovary of Case 1) the layers of a Graafian follicle, (*a*) granulosa cells, (*b*) luteinized theca cells, (*c*) swollen hyperplastic theca cells.

deeply with sudan III. Reticulum fibers were abundant throughout the ovary. Where clear cells were present, it was evident that the fibers surrounded them as a group and not individually (Fig. 2). Graafian follicles were present in abundance. In general they were small in size. In some the various layers were atrophied while in others there was hyperplasia. The most conspicuous change consisted in the presence

of thick collars of swollen theca cells about follicles, indicating definite hyperplasia of this layer (Fig. 3). A moderate number of these cells were polyhedral and clear, not unlike in appearance those of the clear cell islands. No remnants of corpora lutea were found in the ovary despite the fact that it had been completely sectioned.

CASE 2.—R. M., 36-year-old female, was admitted to St. Vincent's Hospital Dec. 13, 1939, complaining of backache, menstrual irregularity, and hirsutism. She was gravid ii, para i. The second pregnancy was terminated by induced abortion. In 1933 she became conscious of thinning of the scalp hair. Concomitant with coarsening of the remaining body hairs, she developed facial hirsutism, progressing until 1937 when she resorted to daily shaving. The hair on the rest of her body also increased in amount. Shortly after this, the menstrual flow became scant. For about four years she had periods of amenorrhea, varying from two to twelve months. In 1938 she was given injections for the amenorrhea. Her periods became re-established for a short time. The last menstrual period was Nov. 20, 1938, lasting three days. Her period previous to this was October 7, lasting eight days and profuse. In the past year her breasts diminished in size. In 1935 her weight was 230 pounds. By means of thyroid extract she managed to reduce.

The patient was well developed and moderately obese. The hair covering her head was thick and coarse. The face was covered with a heavy growth distributed about the chin and upper lip. The neck was short and thick. Both breasts were pendulous. The lungs and heart appeared normal. Blood pressure was 110/64. There was moderate obesity of the chest and abdomen. A few striae gravidarum were present. There were no palpable abdominal masses. There was diffuse hair distribution on the extensor aspect of both upper and lower extremities. Pelvic examination revealed a normal-sized clitoris and normal uterus. Both ovaries appeared enlarged.

Laboratory Data.—Urinalysis was negative. Glucose tolerance test: fasting, 79; half hour, 177; one hour, 200; 2 hours, 125; 3 hours, 76; 4 hours, 62 mg. per cent. White blood count was 9,840; 82 per cent polymorphonuclear leucocytes; 1 eosinophile; 13 lymphocytes; and 4 monocytes. The blood Kahn was negative; nonprotein nitrogen, 25 mg. per cent; and the basal metabolism, plus 3. Aerogram of the adrenal areas was negative. X-ray of the sella turcica revealed no abnormalities.

Operative Findings, Dec. 30, 1938.—The uterus was normal. Both tubes and ovaries were prolapsed and densely adherent. The ovaries were large, white, hard, resilient and completely covered by adhesions. Except for adhesions the tubes were normal. The operation consisted of bilateral salpingectomy and oophorectomy. The endometrium was curetted. It was noted that the patient was bleeding and that this had started the day before.

Following the operation, the patient noted that the hair of the scalp stopped falling out. She also believed that her facial hair grew more slowly so that she did not shave for a week.

The patient has been followed for four years. Her hirsutism persists although she still feels that the rate of growth has been slowed up so that she does not have a shave as often as she did before the operation. She remains moderately obese. Her chief complaint is backache and leucorrhea which she had previous to her operation. She has been attending the out-patient department constantly. Aerograms were re-

peated but revealed nothing unusual.   In summary, about the only change that followed removal of the ovaries was that instead of shaving every day she now shaves twice a week.

Pathologic Report.—Examination of the endometrium revealed it to be in the menstruating state.   The left ovary was large, measuring 7½ by 3½ by 2½ cm.   It was oval in shape and felt firm.   The surface was smooth but nodular.   On section, the ovary for the most part was solid
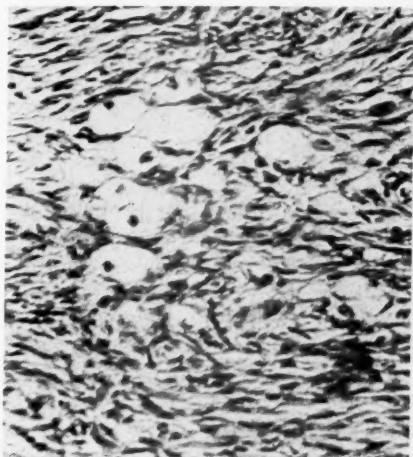

Fig. 4.—Islands of clear cells found in the ovarian stroma (ovary of Case 2).
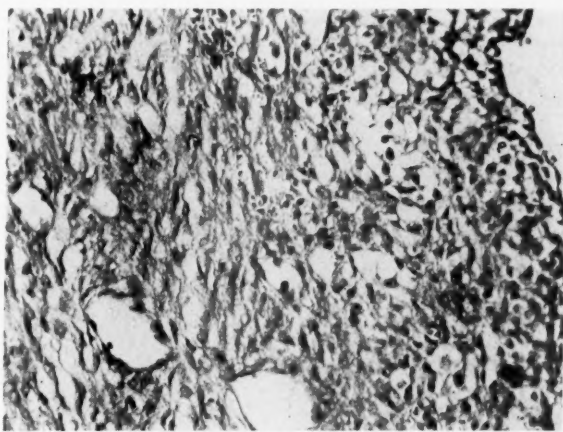
Fig. 5.—Photomicrograph of layers of a Graafian follicle (ovary of Case 2).   Legends and changes same as Fig. 3.

and gray in color.   Small cysts were present in the cortex.   At the approximate junction of the cortex with the medulla, the tissue assumed a yellow orange color.   Toward the center, the ovary was pearly gray and softer in consistency than the cortex.   The right ovary was enlarged, weighing 35 Gm. and measuring 6 by 3½ by 2 cm.   Its surface was likewise nodular but smooth.   The cortex was composed of solid, homogeneous tissue with a light yellow tint.   Both Fallopian tubes appeared normal.

Microscopic Findings.—Both ovaries presented a similar appearance. Their enlargement was due to diffuse hyperplasia of stroma cells. After considerable search, several small nests of clear cells similar to those of Case 1 were found (Fig. 4). Graafian follicles were numerous and most of them atretic. A few exhibited definite, pronounced hyperplasia of theca cells (Fig. 5). Some of these cells were enlarged, polyhedral, and clear. Reticulum was abundant throughout the ovary. Sudan III revealed a small amount of extracellular, finely granular, sudanophilic material.

Comment

Our cases are similar to those reported by Geist and Gaines, displaying obesity, hirsutism, and amenorrhea. One had hypertension. The removal of the ovaries produced no striking changes. Though both patients thought they shaved less often, the hirsutism persists. It should be mentioned that in Case 1 there was an immediate and complete disappearance of the primary complaint, namely, headache. The hypertensive state, however, remains. It is apparent, therefore, that the symptoms of masculinity and the state of hypertension cannot be ascribed to the ovary. The ovarian findings in both of our cases were identical, with the exception that in Case 2 nests of clear cells were very scant, and theca layer hyperplasia was observed in only a few follicles.

One cannot help but wonder as to the causation of the stroma cell hyperplasia, the theca cell proliferation and the identity, origin, and life cycle of the clear cell islands. Do the latter arise from stroma cells, does the presence of fat represent luteinization, or is it a regressive phenomenon, a form of fatty degeneration? We certainly do not have the answer. When Case 2 first came to our attention, its classification presented a perplexing problem. Temporarily it was catalogued as bilateral fibroma of the ovary. Later, when we read Traut and Marchetti's[3] study of granulosa and theca cell tumors, we attempted to fit our cases into their group of pure lipoid-free thecoma. In due course of time, when the ovaries of Case 1 were submitted to us, the problem of classification was reawakened. We submitted slides of these to Traut.* From his study he came to the conclusion that it, represented partial luteinization of a theca cell tumor. Schiller,* on the other hand, influenced by the masculinity of the patient, diagnosed the clear cells as inclusions of adrenal cortical cell origin. Novak* who was also kind enough to study a section from Case 1 pointed out the similarity in appearance between the clear cells of the theca zone of atretic follicles and those of the cell islands and suggested that they might be luteinized granulosa cells. Plaut* noted the striking resemblance of the "clear cell islands" to the "interstitial gland" observed in rabbits. In our own opinion the findings in these cases do not represent a tumor but are a proliferative phenomenon induced by an endocrinologic imbalance affecting among other organs the ovarian stroma, some of whose cells undergo further change as evidenced by the appearance of fat. Hyperplasia and luteinization of cells of the theca layer probably are manifestations of the same phenomenon modified somewhat by the proximity of these cells to the ovum.

References

1. Geist, S. H., and Gaines, J. A.:   Am. J. Obst. & Gynec. 43: 975, 1942.
2. Bergstrand, H.:   Virchows Arch. Path. Anat. 293: 413, 1934.
3. Traut, F. H., and Marchetti, A. A.:   Surg., Gynec. & Obst. 70: 632, 1940.

*Personal communication.

POLYNEURITIS OF PREGNANCY

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OBSTETRIC textbooks and literature contain very little about polyneuritis of pregnancy. However it is now recognized that the polyneuritis which may accompany or follow hyperemesis gravidarum is a dietary deficiency disorder, secondary to the vomiting and due to hypovitaminosis (vitamin B_1). According to Peters[1] in B_1 deficiency there is a defect in the oxidation of the carbohydrate intermediate substance in nerve tissue, particularly pyruvic acid. B_1 is the catalytic agent which completes this oxidation and the removal of the pyruvic acid.

Strauss[2] states that alcoholic polyneuritis, the toxic polyneuritis of pregnancy, diabetic, biliary, and gastrogenous polyneuritides, post-infectious polyneuritis, the Korsakoff syndrome and other similarly misleading names have concealed the true diagnosis of vitamin B_1 deficiency. He believes that these polyneuritides are clinically and pathologically identical with beriberi, differing only in the particular mechanism by which the deficiency is brought about. He states that the pregnant woman when nauseated often restricts her diet to concentrated carbohydrate foods low in vitamin B_1 content, and because of vomiting, fails to retain all that she ingests. Furthermore, her metabolism, and with it her vitamin B_1 requirement, is elevated during gestation, and it is possible that her powers of assimilation are reduced.

With the help of recently developed methods of determination of vitamin B_1 in the urine, it has been shown that there actually exists a marked vitamin B_1 deficiency in polyneuritis of pregnancy. Hildebrandt and Otto[3] reported the complete absence of thiochrome in the urine in a case of severe polyneuritis of pregnancy. Vitamin B_1, however, could be demonstrated after large doses of injected vitamin B_1 shortly before and after delivery. Stähler[4] comes to the same conclusion in his study on healthy pregnant women and those afflicted with polyneuritis of pregnancy. He found a deficit of 36 mg. in one such case.

Iswariah and Kutumbiah,[5] in 1934, stated that in India peripheral neuritis was common during the puerperium in endemic areas of beriberi. These cases differed, however, in their clinical picture from those of true beriberi. An endocrine imbalance was suggested as a precipitating factor.

Berkwitz and Lufkin,[6] in 1932, collected over 500 cases of polyneuritis of pregnancy dating as far back as 1854, but of these only 52 cases were undoubted, four of which were personal observations reported in detail. Plass and Mengert,[7] in 1933, gave a critical review of 28 accepted cases of polyneuritis of pregnancy, adding 12 cases of their own to 16 cases previously reported. Since 1933 a number of other cases have been reported. Lubin and Newman[8] reported a case of their own and mentioned cases reported by seven other authors since 1932. Among others, cases have also been reported by Luikart, Schaupp, Gerstle and Lucia,[9] and most recently McGoogan[10] reported a series of 15 cases.

From a study of the literature it is concluded that the milder cases were carried to term successfully by the use of vitamin therapy. In the

more severe cases, interruption of pregnancy was resorted to in addition to vitamin therapy. It is noteworthy that only few fatalities occurred in the cases reported by various authors during the last ten years (according to McGoogan only 7.5 per cent of those treated with vitamin B_1), although it must be taken into consideration that some of these cases were only mild.

There are only a few autopsy reports of cases of polyneuritis of pregnancy, and our knowledge of morphologic changes in the central and peripheral nervous system in particular is limited. Our observations on a case of polyneuritis of pregnancy, including a complete post-mortem examination, therefore, seemed justified.

Case Report

A primipara, aged 27 years, textile worker, had always enjoyed good health. Her past history, as given by the family, was essentially negative. There was no history of alcoholism, diabetes, or exposure to lead or other metals.

Two or three weeks after her last menses she developed severe nausea and vomiting and three weeks later was hospitalized in a near-by town. The nausea and vomiting persisted, but improved enough for patient to be discharged. However, it was necessary to re-hospitalize her for a period of ten days to two weeks on two or three occasions thereafter. She was treated symptomatically and with intravenous fluids. Approximately four to six weeks after the onset of nausea and vomiting she developed pain in the extremities, especially in the legs. Soon she had some limitation of motion of the arms and legs, and suffered great pain when touched. She was hospitalized for this condition, and treated for a period of one week with daily intramuscular injections of 2,000 international units of thiamin chloride. After two weeks she was discharged "greatly improved, but not entirely free from pain." Thereafter, she remained at home in bed, suffering severe pain in the extremities, was unable to use the extremities properly, and was extremely confused mentally. She suffered from headaches and blurring of vision. Moderate swelling of the ankles persisted. During the month prior to her last hospitalization she did not vomit, and managed to eat fairly well, although she was unable to use her hands to feed herself. Her home physician had given her considerable sedation, both by mouth and hypodermically, and while under the influence of these drugs she was comparatively quiet. More recently she experienced some vesical and rectal incontinence.

When I first saw the patient on Aug. 9, 1941, in the Charlotte Memorial Hospital, physical examination revealed the following findings: The patient was of medium build, well developed, appeared semistuporous and mentally confused. There was little evidence of dehydration; her temperature was 99.3° F. The head and eyes were grossly negative, and the ophthalmoscopic examination revealed normal fundi. The teeth were in fair condition. The thyroid appeared normal. The chest was entirely negative except for a moderate tachycardia. The systolic blood pressure was 120 mm. of mercury and the diastolic 80 mm. On abdominal examination, the uterus was felt just below the umbilicus. The fetal heart sounds could not be heard, and no fetal movements were perceived. Vaginal examination revealed a uterus enlarged to the size of a four or four and one-half months' pregnancy.

Examination of the extremities revealed limited mobility of all four extremities, and inability to lift the arms to a vertical position. There was no swelling of the joints, but there was considerable tenderness and hyperesthesia over the joints and all parts of the extremities. A diagnosis of polyneuritis of pregnancy was made.

After a neurologic examination was made, Dr. T. W. Baker reported the following: "There is no evidence of any cranial nerve paralysis. There is a marked weakness of all the extremities which seems symmetrical and equal. The patient is barely able to move the toes, but some quadriceps and psoas power in both legs is preserved. There is very little use of hands and fingers, and the hand grip is nearly absent. There seems to be fair use of the proximal muscles of the shoulder girdle. Exquisite tenderness of the calves to pressure is elicited. The reflexes of the lower extremities are entirely absent except for a slight flicker of the left Achilles reflex. The reflexes of the upper extremities are fairly normal and equal. The Babinski phenomenon is absent. There is undoubtedly some sensory loss in the feet, legs, and hands, but the extent is impossible to determine with the confused and uncooperative mental state of the patient." It was his opinion that the patient was probably suffering from polyneuritis of pregnancy, following hyperemesis gravidarum.

The laboratory findings on admission were as follows: Urine: Specific gravity, 1.012; reaction, alkaline; albumin, one-plus; sugar, negative; microscopic, few white blood cells and epithelial cells. (Catheterized specimen.) Blood counts: Hemoglobin, 62 per cent; red blood cells, 3,550,000; white blood cells, 8,700; differential: 69 per cent polymorphonuclears, 10 per cent stabs, 15 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophiles. Serology: Kahn, negative. Blood chemistry: nonprotein nitrogen, 32.9 mg. per cent; cholesterol, 235 mg. per cent; total protein, 7.2 Gm. per cent; icterus index, 4. Gastric analysis: Normal amount of free hydrochloric acid present, using histamine as a stimulus. Spinal fluid: Normal pressure (125 mm.); color, clear; total protein: 62.5 mg. per cent; globulin, normal; cell count, one lymphocyte present; Kahn and colloidal gold, negative. Cervical smear revealed many gram-positive bacilli, many epithelial cells, and a few pus cells. Culture: revealed lactobacilli. The electrocardiogram revealed only tachycardia.

Treatment during the next ten days consisted of vitamin B_1 (thiamin chloride), 200 to 250 mg. intramuscularly or intravenously daily, plus polyvitamins (especially riboflavine, 10 mg. daily, and nicotinic acid, 200 mg. daily) by mouth, iron (ferrous sulfate) by mouth, and liver injections daily. A diet of lean meats, vegetables, fruits, and milk was forced. It was necessary to resort to frequent sedation to keep the patient quiet. She was mentally confused and irrational most of the time, and would cry or scream throughout the night. During the ten-day period of observation, the strength of the extremities definitely improved, but there was no change in her general condition. Involuntary stools and voiding were almost constant. A low grade temperature was constantly present.

In view of the symptoms, interruption of pregnancy was believed to be indicated, although it was doubtful that it would alter the course of the disease at this stage.

Following preparatory blood transfusion, pregnancy was interrupted by a vaginal hysterotomy, performed under cyclopropane anesthesia.

Considerable operative difficulty was encountered, due to a high rigid cervix and the nonelasticity of the tissues and supporting structures. Nevertheless, the patient stood the procedure well. Bleeding was minimal, and the patient returned to her room in fairly good condition. However, within a few hours it was evident that the patient was not doing well. The temperature had risen to 104° F., pulse rate 140, and respirations 34 per minute. She became very noisy and completely irrational. Sedation in extremely large doses was necessary. Twenty-four hours after the operation the temperature was normal, but during the day spiked to 104.2° F., and during the next three days it ranged from 101° to 104° F. Blood transfusion was repeated. Glucose and saline were given intravenously and by hypodermoclysis. The patient developed great difficulty in swallowing. Blood culture was negative. Six grams of sodium sulfapyradine were given intravenously. Finally death occurred on the fourth postoperative day, being preceded by a terminal pulmonary edema.

The necropsy, performed by Dr. Paul Kimmelstiel, revealed the following findings:

Anatomic Impression: Status postabortum. No gross pathologic findings.

Histologic Examination.—(Significant findings only.) *Heart:* Five sections through different portions of the heart muscle failed to reveal evidence of histopathologic changes. It was noteworthy that there was no "hydropic degeneration" of the heart muscle as described in beriberi hearts. *Lungs:* There were minute areas of aspiration and bronchopneumonia.

Adrenals: There were several foci in the zona fasciculata in which adrenal epithelial cells showed degenerative changes to the point of actual necrosis, granulation and disintegration of their cytoplasm. The areas were characterized by a rather massive infiltration with polymorphonuclear leucocytes. *Kidneys:* There was some acute dilatation of the tubules and very slight interstitial edema with round cell infiltration.

Uterus: The endometrium contained placenta and decidual tissue. Chorionic elements were seen to penetrate into the superficial layer of the muscularis. The inner surface was covered with fibrin and blood. Otherwise the organ was negative.

Sciatic Nerve: Myelin sheath stain revealed several areas in which the nerve fibers were disintegrated, having lost their myelin sheath, were blown up balloon-like. Fat stains showed in some areas the presence of numerous fat containing macrophages in between the nerve fibers.

Brain: A number of blocks were fixed in alcohol, embedded in celloidin, and stained by the Nissl method. A careful search was made for degenerative changes in ganglion cells. The following blocks were taken: three different portions from the cortex, three different levels of the basal ganglia, one section through pons, medulla oblongata, cerebellum, and three different levels of the spinal cord. The ganglion cells were clearly stained, but no change in the tigroid substance of any other pathologic change was seen in the ganglion cells, glia, or mesoderm. Spielmeyer stains on sections taken from three different levels of the spinal cord failed to reveal evidence of degeneration of the myelin sheaths.

Histologic Interpretation.—From histopathologic point of view only two positive findings of significance can be stated.

1. Degenerative changes in the peripheral nerves (sciatic nerve).

2. Recent cortical necrosis in the adrenal with polymorphonuclear leucocytic infiltration.

It is noteworthy that the myocardium fails to reveal vacuolization as described in beriberi. Also an exhaustive study of the central nervous system does not show degenerative changes as described in vitamin B_1 deficiency.

Comment

A case of polyneuritis of pregnancy in a late stage of the disease is reported in which death occurred notwithstanding treatment with massive doses of vitamin B_1 and interruption of the pregnancy.

It can hardly be denied that polyneuritis of pregnancy represents a manifestation of vitamin B_1 deficiency. Therapeutic results and biochemical determinations of thiochrom output in the urine constitute convincing evidence. The finding of degenerative changes in the peripheral nerves in our case confirms this assumption.

· It may be noted, however, that the organic changes which are usually observed in similar cases of profound depletion of vitamin B_1 are absent. Although myocardial damage and degenerative changes in the central nervous system may be absent in vitamin B_1 deficiency, it is generally assumed that death in beriberi is due to cardiac damage and subsequent circulatory failure. Our patient showed no signs of this throughout her illness, nor was there evidence of circulatory impairment or vacuolization of myocardial muscle fibers at autopsy.

It is furthermore noteworthy that a careful study of the central nervous system failed to reveal evidence of degenerative changes, particularly in the spinal cord. The autopsy findings, therefore, though compatible with vitamin B_1 deficiency, are not characteristic of those cases in which death is due to beriberi. The rather extensive acute necroses in the adrenal cortex may be significant in regard to the mechanism of death, but since no mention of such changes is made in previous reports, no comment is made at this time.

Not much improvement could be expected from specific therapy in the advanced stage in which the patient came under our observation. Although actual degenerative changes in the spinal cord and ganglion cells are not observed, it must be assumed that in later phases of polyneuritis of pregnancy the peripheral neurodegeneration becomes practically irreversible in spite of massive and continuous doses of vitamin B_1. Others have pointed out that involuntary micturition and defecation must be taken as ominous signs, indicating that apparently the threshold of repairability has been passed. The experience in our case seems to confirm this observation.

In a case of this type when the physician apparently faces insurmountable difficulties he may, as we did, resort to interruption of pregnancy, although this procedure admittedly has no clearly defined specific rational indication other than the thought that a disease precipitated by pregnancy may be influenced by its interruption. It is, however, possible that this procedure may hasten the death of the patient as it probably did in our case. This experience seems to bear out McGoogan's conclusion that "therapeutic abortion is contraindicated in polyneuritis of pregnancy."

References

1. Peters, R. A.: Lancet 1: 1161, 1936.
2. Strauss, M. B.: J. A. M. A. 110: 953, 1938.
3. Hildebrandt, A., and Otto, H.: München. med. Wchnschr. 85: 1619, 1938.

4. Stähler, F.: Deutsche med. Wchnschr. **64:** 1137, 1938.
5. Iswariah, V., and Kutumbiah, P.: Indian M. Gaz. **69:** 13, 1934.
6. Berkwitz, N. J., and Lufkin, N. H.: Surg., Gynec. & Obst. **54:** 743, 1932.
7. Plass, E. D., and Mengert, W. F.: J. A. M. A. **101:** 2022, 1933.
8. Lubin, Samuel, and Newman, N. W.: Am. J. Surg. **45:** 131, 1939.
9. Luikart, Ralph: Nebraska M. J. **23:** 247, 1938.
   Schaupp, K. L.: Quoted by Gerstle, Mark, Jr., and Lucia, S. P.: California & West. Med. **40:** 167, 1934.
10. McGoogan, L. S.: Am. J. Obst. & Gynec. **43:** 752, 1942.

LEFT-SIDED PELVIC LESIONS SUBSEQUENT TO APPENDICITIS

Report of Three Cases

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APPENDICITIS in some of its protean manifestations frequently interests the gynecologist. Problems in differential diagnosis between appendicitis and primary salpingitis, tubal pregnancy, renal colic, etc., occasionally arise. During the course of severe appendicitis in women, the cul-de-sac of Douglas may be the site of abscess formation either before or after the removal of the appendix. Appendicitis as a source of infection causing tubal closure and sterility is probably common. Severe damage to the right adnexal structures from inflammations primary in the appendix is well known.

Less frequently reported, because less common, is left-sided abdominal and pelvic infection during or subsequent to inflammations of the appendix. Nather[1] reports 9 such left-sided abdominal abscesses occurring during the course of appendicitis. He emphasizes the greater frequency of extension to the left side in children and points out the peculiar anterior position against the abdominal wall of at least a portion of the left-sided abscess. The mechanism of formation of such abscesses is reviewed. The most tenable idea seems to be that from a medially placed inflamed appendix exudate is shunted to the left abdomen over the superior surface of the bladder.

The purpose of this paper is to report observations on three young women who were seen with lesions in the left pelvis not during acute appendicitis but four years, eight months, and twenty-four years, respectively, subsequent to their first attacks. The impression is not meant to be conveyed that the right adnexal structures escaped all damage, but certainly the major lesions outside the unrecognized appendicitis were in the left pelvis only, and in all three this was true from the time they were first seen. The third with appendicitis twenty years before as a child, probably had peritonitis and more than left-sided abscess formation at the time of her attack.

Report of Cases

Case 1.—D. P., an Italian girl, aged 15 years, single, entered the hospital complaining of lower abdominal pain, nausea, and occasional

vomiting, for five days. For four years there had been attacks of right lower quadrant pain with nausea. On six occasions during the last ten months she had been seen in the out-patient department with lower abdominal pain and a diagnosis of salpingitis was made. Since the hymen was intact, and there were no stigmas of lower genital tract gonorrhea, the tubal lesions were thought to be tuberculous.

On admission, the white blood count was normal and there was no fever. The erythrocyte sedimentation rate was rapid. On rectal examination there was a mass in the left fornix 5 cm. in diameter, with slight induration to the right of the uterus.

At operation an abscess containing a few drams of pus was encountered in the left pelvis anteriorly. Both tubes were inflamed but patent. The operator still believing the infection to be an acute tuberculosis removed both tubes. After completing the pelvic operation, the cecum was delivered, and the appendix was found to be thick and indurated with a perforation in its middle third tightly walled off by omentum. It was removed.

Except for moderate infection of the incision the patient made a good recovery.

CASE 2.—J. H., a school girl, aged 15 years, entered the hospital complaining of attacks of vomiting and progressive weight loss for eight months. The patient was in school through this time, except on the average of every month to six weeks she was in the school infirmary for one or two days with vomiting and pain in the lower abdomen. The pain recently had become localized to the left lower abdomen. During these attacks she was seen by two or three different physicians and no definite diagnosis was ever established. After eight months, at the close of school, there was a weight loss of twenty-five pounds. At no time was she known to have fever or leucocytosis.

On admission, the leucocyte count was 9,100, and hemoglobin 67 per cent (Sahli). There was a slight tenderness over the lower abdomen with an ill-defined mass deep in the left pelvis above Poupart's ligament. The hymen was intact. On rectal examination, the mass in the left fornix was irregular, hard, firm, and measured 10 by 8 by 8 cm. There had been slight irregularity and some increase in menstrual flow. For this reason mainly, a diagnosis of a solid left ovarian tumor was made, having in mind granulosal cell tumor.

At operation a hard, indurated tuboovarian inflammatory mass with a small abscess anteriorly was encountered in the left pelvis. The right tube and ovary were mildly involved in fibrous adhesions. The appendix was found to be thick and indurated with a perforation in its middle third lightly sealed off by omentum. The left tube and ovary, being completely destroyed, were removed, and an appendectomy was done.

Recovery was uneventful except for moderate infection of the incision.

CASE 3.—G. B., a college student, 23 years of age, entered the hospital with no complaints. A few days previously on routine physical examination in the student health clinic she was told she had a large ovarian cyst. On examination, the abdomen was rounded below the umbilicus with a definite cystic tumor in that region. The hymen was intact. On rectal examination the rather flaccid cyst seemed to fill the left fornix, was partially fixed, and was assumed to be of left ovarian origin.

At operation a large, flaccid, thin-walled adherent tuboovarian inflammatory cyst on the left was encountered with part of the cyst intraligamentary. The right tube and ovary were surrounded with fibrous adhesions, but the tube was patent. Upon investigation of the appendix, it was found that it had spontaneously amputated itself at some time in the patient's life. At the base there was a stub 1 cm. long completely sealed over except for a thin fibrous cord representing the remainder of the appendix. The region of the cecum was fairly free of adhesions. The cyst, made up of the left tube and ovary, was removed, and the residual of the appendix amputated inverting the stump as usual.

Upon study of the cyst the criteria for tuboovarian inflammatory cyst seemed to be fulfilled. The lumen of the dilated tube communicated with the cystic cavity and the only lining was a very flat serous epithelium. The tubal fimbriae could not be found flattened out inside the cyst.

After operation it was learned from the patient's sister that at the age of four years there was a serious illness diagnosed as appendicitis and peritonitis. The patient was never operated upon because it was thought she was too ill. After many weeks, recovery from the illness was apparently complete.

Recovery from the operation was uneventful.

Summary

Two cases of chronic left tuboovarian abscess and one case of left tuboovarian inflammatory cyst are reported long subsequent to primary attacks of appendicitis.

In young women appendicitis as a source of even left-sided pelvic lesions must be borne in mind.

Reference

1. Nather, C., and Ochsner, A.: Surg., Gynec. & Obst. 40: 495, 1925.

PROLAPSE OF THE FIMBRIATED END OF THE FALLOPIAN TUBE THROUGH OPERATIVE SCAR IN ANTERIOR VAGINAL WALL

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ON SEPT. 20, 1940, Mrs. C. R., a 41-year-old, syphilitic (Wassermann 2-plus), 98 pound, married female, gravida v, para v, was admitted to the surgical division of St. John's Hospital. Her chief complaint was pelvic discomfort of two years' duration.

The outstanding pathologic conditions found were as follows: marked pelvic floor relaxation due to old lacerations and multiple deliveries, with large cystocele and rectocele, first-degree prolapse of the uterus, a large, markedly lacerated cervix with endocervicitis, and a small umbilical hernia.

On Sept. 23, 1940, the following procedures were performed : (1) high amputation of the cervix, (2) anterior colporrhaphy with interposition of the uterine fundus, (3) sterilization by resection of the tubes at the cornual ends and burying cut ends between the folds of the broad ligament, (4) posterior colporrhaphy, and ,(5) plastic repair of the abdominal wall for the small umbilical hernia.

For the first four days postoperatively there was a moderately severe febrile reaction due to an infection in the right broad ligament, the induration being palpable along the course of the round ligament in the right inguinal canal. No evidence of any intraperitoneal infection was present at any time. From the second day on there was a bloody, purulent and foul vaginal discharge with a secondary hemorrhage estimated at about three ounces occurring on the seventh day postoperatively; a speculum examination failed to reveal the site of the bleeding or source of the vaginal discharge. The hemorrhage did not recur and by the fourteenth day postoperatively the vaginal discharge had ceased. The temperature subsided gradually as did the local and general systemic reaction from the fifth day onward and by the thirteenth day the temperature was normal and remained so. The patient was out of bed on the sixteenth day.

On Oct. 10, 1940, the seventeenth day postoperatively, examination revealed a clean, well-healed cervical stump, an apparently well-healed anterior vaginal wall, the interposed uterine fundus in excellent position, a firm well-healed pelvic floor with only a small superficial unhealed skin area in the perineum, and a well-healed abdominal wall with obliteration of the umbilical hernia. The patient was discharged from the hospital as cured on Oct. 15, 1940, twenty-two days postoperatively.

Early in January, 1941, the patient was seen in the out-patient department of the hospital. She was complaining of vaginal discharge. She was readmitted to my service on Jan. 8, 1941.

Findings on second admission : The blood Wassermann was now four-plus. On the anterior vaginal wall there was an elevated mass projecting about one-fourth of an inch above the surface. It was about ¾ to 1 inch in diameter and situated directly in the midline of the vagina about one-half inch above the urethral orifice in the site of the anterior colporrhaphy scar (Fig. 1). The interposed uterine fundus was palpable beneath the adjacent vaginal wall. The tumor was a dusky red in color, its base was sessile and firmly attached to the vaginal wall. The surface of the tumor was slightly irregular and nodular and bled on the slightest touch. The following opinions were expressed : (1) squamous cell carcinoma arising in an operative scar, (2) granuloma, possibly syphilitic, ,(3) endometrioma from endometrial transplant from cornua of uterus.

Biopsy was done on Jan. 13, 1941. The unexpected findings are shown in Fig. 2. The mass was held with sponge forceps and an elliptical incision made through the vaginal wall (Fig. 2, 1). With only slight traction on the mass, the Fallopian tube and a small amount of broad ligament were delivered (Fig. 2, 2). The tube and broad ligament were ligated about one-half inch from the point of vaginal exit (Fig. 2, 3) ; the ends of the suture were then used to bury the stump, fix it to the under surface of the vagina and close the small vaginal

incision (Fig. 2, *4*).   A heavy purse-string suture was then placed around the closed incision, the vagina scarified (Fig. 2, *5*) and the suture tied (Fig. 2, *6*).

Histologic examination of the structure just below the mass showed typical Fallopian tube.   The mass itself showed the fimbriated end of
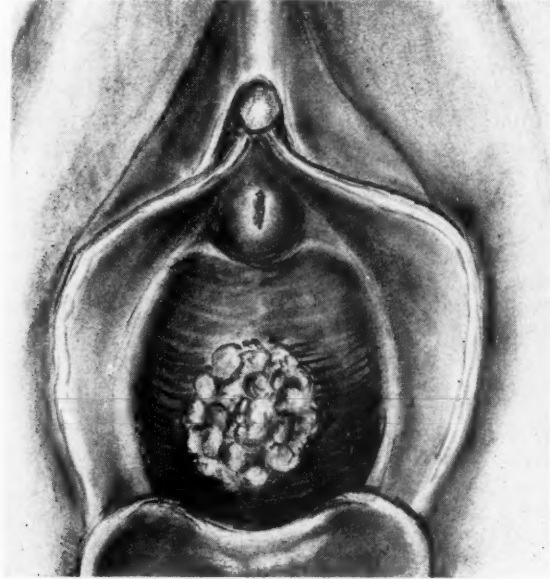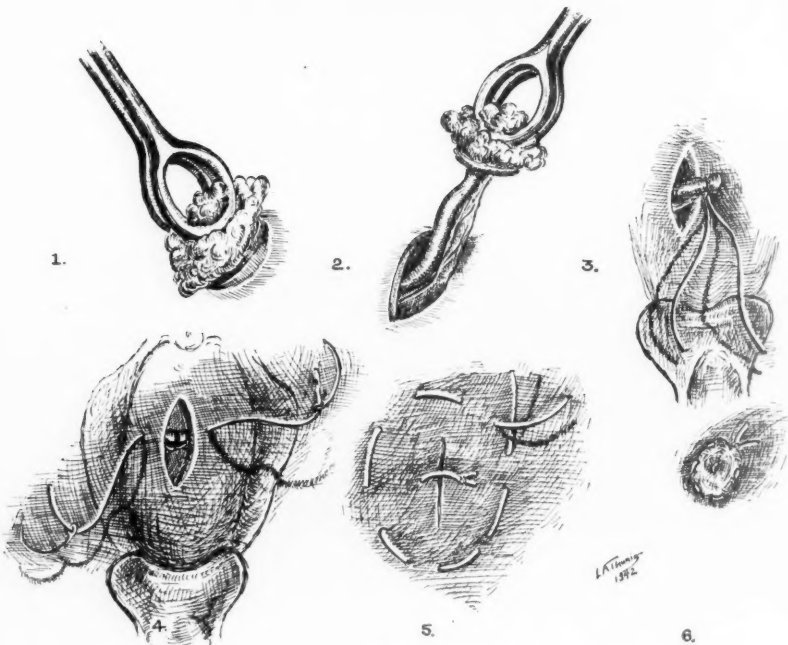

Fig. 1.

Fig. 2.

tube markedly changed in its histology because of infection and granulation.   The individual fimbriae were no longer discernible as such.

The postoperative course was uneventful and the patient was discharged Jan. 19, 1941, six days postoperatively.

Discussion

To judge solely from the number of cases reported in the literature, the condition is very rare.   The author found only five case reports by four writers.[1-4]   However, from Kennedy and Campbell's book one gets the impression that prolapse of the tube as a complication of vaginal hysterectomy, at least, is not at all uncommon.[5]

With one exception, every case reported or spoken of has followed vaginal hysterectomy, some of which were drained.[1, 2]   The exception followed a posterior colpotomy for ectopic in which unusual drainage was used.[4]   In the case just presented the operation was an interposition procedure with resection of the tubes at the uterine cornua, complicated by the development of a moderately severe infection.

Follow-up examination, Jan. 14, 1943, two years after the second operation, showed the abdominal wall, pelvis, and pelvic floor essentially the same as on Oct. 10, 1940, seventeen days after her first operation.   The anterior vaginal wall is smooth without traces of her second operative scars.

References

1. Bower, J. C., Pearce, A. E., and Conway, E. W.:   Am. J. Obst. & Gynec. 40: 1047, 1940.
2. Radman, H. M.:   Am. J. Obst. & Gynec. 42: 143, 1941.
3. Pozzi: Compt. rend. Soc. d'obst. de gynéc., Paris 4: 255, 1902.
4. Moulonguet, P.:   Bull. Soc. d'obst. et de gynée. 17: 131, 1928.
5. Kennedy and Campbell: Vaginal Hysterectomy, Philadelphia, 1942, F. A. Davis, p. 172.

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BENIGN PAPILLARY EPITHELIOMA OF THE VULVA

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THE benign papillary epithelioma of the vulva is an extremely rare tumor.

After a careful survey of the literature on benign and malignant epithelial tumors of the vulva, it was noted that comprehensive monographs on vulval disease[9, 16] and skin tumors[4, 6, 14, 17] do not include this tumor among the benign epithelial neoplasias affecting the vulva. Novak[15] and MacCallum[13] have called attention to the "rare true papilloma" of the vulva, but a histologic description and pathologic differential diagnosis were not submitted in their texts.   In a recent publication Folsome[5] also mentioned the true papilloma, but histologic details were omitted.

Kehrer[10] has described 3 cases of benign papillary epithelial tumors of the vulva.   He distinguished them sharply from condylomata acuminata and called them verrucous papillomata.   Kehrer also cited 5 similar cases[1-3, 7, 11] which he had encountered in the literature, but

a histologic description or microphotographs of these cases were not available for study. R. Schroeder (quoted by Kehrer[10]) resected a similar tumor, which recurred in the form of a squamous carcinoma.

In a symposium on malignant diseases at the Memorial Hospital, New York, Healy[8] presented a case of benign epithelial papilloma of the vulva. The patient had suffered from pruritus vulvae for ten years. Treatment consisted of local excision of the bulky, papillary mass. No radiation therapy was given. The patient died five years later of a cerebral accident, and follow-up study during the five-year period revealed no recurrences.

Case Report

R. D. T., a 36-year-old, white, American, housewife, was admitted to the Beth Israel Hospital on Oct. 24, 1940, complaining of a "vaginal tumor" of four months' duration and pruritus vulvae of one year's duration.

Present Illness.—About one year ago the patient was hospitalized for pulmonary tuberculosis and shortly after developed pruritus vulvae. Upon discharge from the hospital six months later, she consulted a physician, who told her she had a "vaginal tumor." There has been no dyspareunia, vaginal discharge, or pain in the groins or thighs. The only complaint referable to the tumor was constant itching of the vulva, which was worse at night.

The family history was irrelevant.

Past History.—The patient had suffered with bronchial asthma for twenty-six years. She has had 8 attacks of pneumonia, the last attack occurring eight years ago. Tonsillectomy was performed at the age of 27 years. Menstruation began at the age of 14, recurred every twenty-six to twenty-eight days, and the duration of the flow averaged three and one-half days. Bleeding was moderate and not associated with pain. The last menstrual period occurred Oct. 30, 1940. During the period of hospitalization for tuberculosis, the patient had an amenorrhea of three months' duration. She had been married ten years, had never been pregnant, and had not resorted to contraceptives.

Physical Examination.—Except for an edentulous upper jaw, examination of the head and neck revealed nothing of note. Variously pitched squeaks and râles were audible over the entire chest, and the breath sounds at the right base had a bronchoamphoric quality. The heart was not remarkable. The blood pressure was 118 mm. systolic and 64 mm. diastolic. No abdominal masses were palpable. There was no inguinal adenopathy. The fingers were clubbed.

The upper two-thirds of the right labium minus, part of the clitoris, and the upper end of the left labium minus were replaced by an ovoid mass (Fig. 1), which measured 3½ cm. in its long axis and 2 cm. in thickness. The surface of the tumor was irregular and consisted of small papillary masses. It was not tender and did not bleed upon manipulation. Examination of the internal genitals revealed nothing of note.

Urinalysis revealed a trace of albumin. The Wassermann reaction was negative.

Treatment.—On Oct. 25, 1940, the involved area was excised under local anesthesia and the skin closed without drainage. The patient was discharged from the hospital three days later.

Subsequent Clinical Course.—The wound healed by primary intention and the pruritus subsided promptly. Periodic examinations revealed no recurrence or metastases. The patient has not lost weight and aside from asthma has been symptom-free.

Description of Specimen

Gross Appearance.—The specimen consisted of a piece of hairless skin, 5.5 cm. long, up to 1.8 cm. wide. A soft, ellipsoid mass, 3.5 cm. long and about 1.5 cm. high, protruded near its one edge. This mass was sharply demarcated from the skin, partly by a groove which in one place deepened into a pocket almost 1 cm. in depth. The surface of the mass
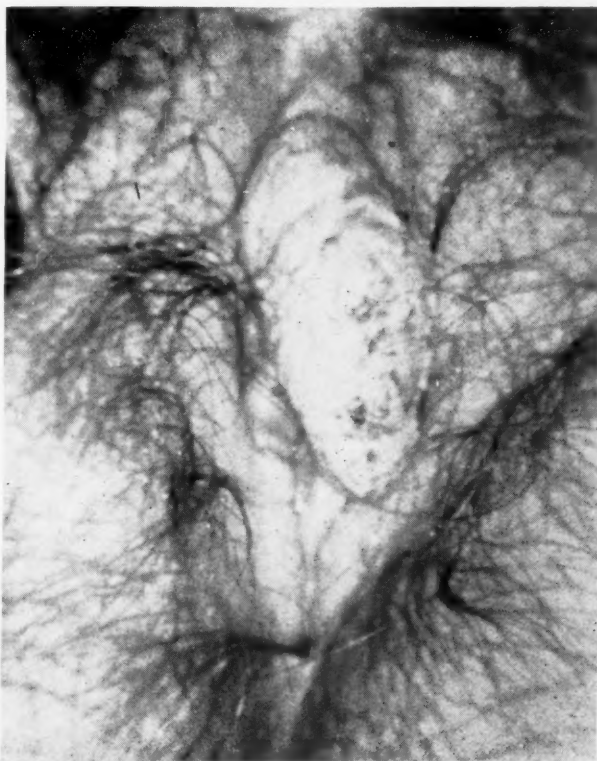
Fig. 1.—Tumor in situ. The ovoid mass is attached by a short pedicle to both labia minora and the clitoris.

was a shaggy whitish gray and consisted of many single finger-like formations packed closely together. The raw surface was formed partly by whitish gray tissue without markings and partly by fat tissue; this surface was concave, the deepest part of the concavity corresponding to the middle of the tumor.

Following fixation, the cut surface appeared as closely packed, finger-like protrusions. In its central portion the tumor had a thickness of 9 mm. The outline against the underlying tissue was straight in the thinner portion and slightly wavy in the thicker one. At one point the outline against the underlying tissue was slightly convex downwards and not entirely distinct.

Microscopic Examination.—Representative blocks of tissue were fixed in formalin and stained with hematoxylin-eosin, van Gieson, iron-hematoxylin, and Weigert's elastica stain.

The picture was that of a papillary epithelial overgrowth with extreme keratosis and parakeratosis (Fig. 2). In some areas the keratotic masses were about twice the thickness of the epithelium. There appeared to be no difference in the degree of keratosis between the papillae as compared with their tips. In some areas the keratosis was seen to involve
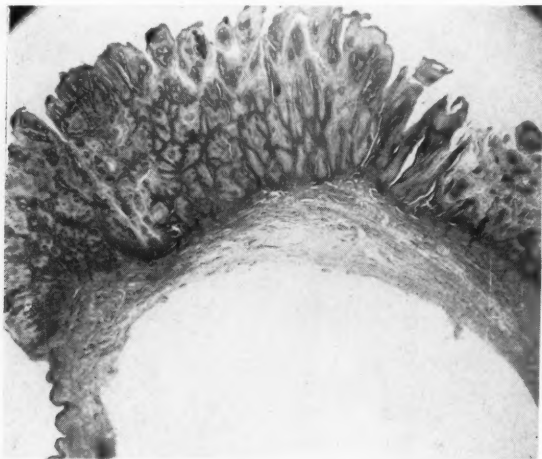
Fig. 2.—Paraffin section; hand lens magnification. The picture is that of a papillary epithelial overgrowth.
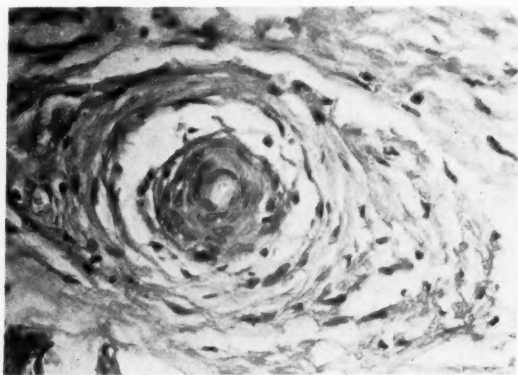
Fig. 3.—Sweat gland duct; its lumen is practically occluded by extensive keratinization.

the sweat gland ducts with apparent occlusion of their lumina (Fig. 3). In other areas the ducts appeared considerably distended. Throughout the papillary portion of the tumor the connective tissue cores were very thin; they contained many wide, thin-walled, mostly empty blood vessels. Occasionally they were hyalinized. The usual configuration of the squamous epithelium was maintained, and there were no abnormalities of cell structure or staining qualities. The intercellular bridges were distinct. The cells of the basal layer were arranged in an orderly manner

and exhibited no evidence of anaplasia (Fig. 4). Although at a few points the basilar portion had a somewhat plexiform appearance, there was no true invasion of the cutis. At the junction between epidermis and cutis, there was considerable infiltration with mononuclear elements and some polymorphonuclear leucocytes. Sweat glands were numerous, and some of them were atrophic. Hair follicles were occasionally seen, but sebaceous glands were sparse.

Discussion

The presence on the labia or mons veneris of an ovoid tumor, whose surface is papillary and nonulcerated, and which is either sessile or attached by a short pedicle, should suggest the possibility of a benign epithelioma. Unlike the condyloma acuminatum, this tumor occurs as a single growth, reaches appreciable size, and according to Kehrer[10] is not associated with a foul odor, as is commonly the case with the condylomata
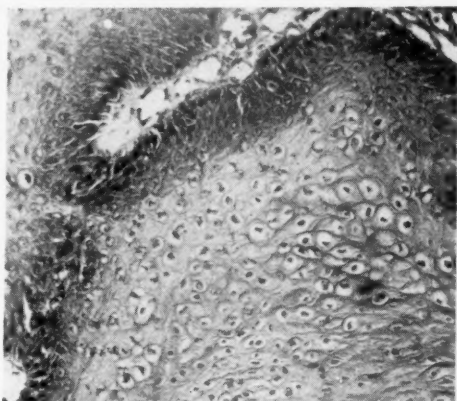

Fig. 4.—A typical portion of the tumor under medium magnification. Note the orderly arrangement of the prickle and basal cells. The connective tissue core is thin and contains numerous empty blood vessels.

acuminata. Histologically the benign epithelioma differs from the venereal wart by the presence of intense keratosis and parakeratosis, absence of edema of the epiderm, little, if any, stigmas of an inflammatory process, and a connective tissue stroma that is not congested.

There is no evidence to indicate that the neoplasm may recur following operative removal or that clinical malignant activity may be expected at some later date. In our tumor, Kehrer's series,[10] and in Healy's case,[8] there were no recurrences or subsequent clinical malignant manifestations. Schroeder's case recurred in the form of a squamous carcinoma. This case was quoted by Kehrer as a benign epithelial papilloma, but a histologic description of the tumor was never recorded in the literature.

Carcinoma-like condylomas of the penis have been described.[12, 18] They have been regarded as benign neoplasias and were called condylomatoid precancerosis by Unna,[18] who, too, regarded them as benign. These penile tumors were characterized by a downward infiltration of the epithelium, attributed to compression by a rapidly proliferating epithelium, and enlargement and differences in staining qualities of the epithelial cells. Such histologic characteristics are strikingly absent in the benign papillary epithelioma of the vulva.

Summary

A case of benign papillary epithelioma of the vulva is described and 4 similar authentic cases are collected from the literature. The tumor occurs as a single, round or ovoid mass, whose surface is papillary and nonulcerated. It is attached to the labia or mons veneris by a short pedicle or it may be sessile. It differs sharply from the condyloma acuminatum, with which it may be confused. The available evidence indicates that the tumor is anatomically and clinically benign.

References

1. Aubenas, G.: Des tumeurs de la vulve, Thèse de Strasbourg, 1860.
2. Benicke: Ztschr. f. Geburtsh. u. Gynäk. 24: 325, 1892.
3. Bursteff: Papilloma teratoides clitoridis, St. Petersburg, 1881.
4. Eller, J. J.: Tumors of the Skin, Benign and Malignant, Philadelphia, 1939, Lea & Febiger.
5. Folsome, C. E.: J. A. M. A. 114: 1499, 1940.
6. Gans, O.: Histologie der Hautkrankheiten, Bd. 2, Berlin, 1928, Julius Springer.
7. Gilette: Am. J. Obst. 12: 599, 1879.
8. Healy, W. P.: Am. J. Surg. 8: 217, 1930.
9. Hunt, E.: Diseases Affecting the Vulva, St. Louis, 1940, The C. V. Mosby Co.
10. Kehrer, E.: Handbuch der Gynäkologie (Veit) Bd. 5, 1929, p. 470.
11. Klob, Julius M.: Pathological Anatomy of the Female Sexual Organs, New York, 1868, Wm. Wood & Co.
12. Loewenstein, L. W.: M. Clin. North America 23: 789, 1939.
13. MacCallum, W. G.: Text-Book of Pathology, ed. 7, Philadelphia, 1940, W. B. Saunders & Co.
14. MacKee, G. M., and Cipallaro, A. C.: Cutaneous Cancer & Precancer, Monograph (Am. J. Cancer), New York, 1937.
15. Novak, E.: Gynecological and Obstetrical Pathology, Philadelphia, 1940, W. B. Saunders Co.
16. Taussig, F. G.: Diseases of the Vulva, New York, 1931, D. Appleton-Century Co.
17. Thomson, Sydney: Tumors of the Skin, Brit. Encyclopedia Med. Practice (Sir Humphrey Rolleston), London, 1939, Butterworth & Co., Vol. 2, p. 200.
18. Unna, P. G.: Die Histopathologie der Hautkrankheiten, Berlin, 1894, A. Hirschwald.

MALIGNANT LYMPHANGIOMA OF THE OVARY

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TRUE lymphangiomas of the ovary are very rare. To date there have been only four cases recorded: two by Kroemer,[1] one by Fleischer,[2] and one by Sidall and Clinton.[3] To this we add one of our own, making the total number of recorded cases five in number. Two cases have been excluded because they arose from dermoid cysts (Schottlaender[4] and Rössle,[5]).

It is our purpose here to report the fifth case of lymphangioma of the ovary, and as far as we know, the first case in which malignant changes were present. Only such data having direct bearing on the neoplasm has been considered.

A colored female, aged 31 years, was admitted on Sept. 21, 1940, complaining of enlargement of the lower abdomen of one month's duration.

A palpable mass was present in the lower abdomen extending to the umbilicus. On Sept. 24, 1940, a large tumor was removed from the left adnexal region and a small portion of the right ovary was resected.

The left ovarian mass measured 15 by 12 by 7 cm. Its external surfaces were gray and smooth. Cut section revealed numerous cysts of varying sizes whose linings were pale brown and smooth and contained a yellowish translucent fluid. A microscopic diagnosis of benign lymphangioma of the left ovary was made (Fig. 1). Unfortunately the resected portion of the right ovary was lost.

The postoperative course of the patient was uneventful and the patient was discharged on Nov. 4, 1940.

On April 8, 1941, the patient was readmitted with abdominal rigidity, pain, swelling and a ballotable mass in the lower abdomen, the size of a four months' pregnancy.

A second laparotomy was performed on April 14, 1941, and revealed about 2,000 c.c. of serosanguineous fluid in the peritoneal cavity. Floating in this fluid were fragments of friable grayish brown neoplastic tissue. A tumor mass filled the pelvis and many other tumor masses were adherent to the small and large intestine, peritoneum, and the liver. The patient gradually became worse and died on April 22, 1941.

Autopsy showed all the abdominal viscera obscured by large masses of hemorrhagic grayish friable tissue which were attached to the peritoneum, liver, spleen, and intestine.

The pleural surfaces were smooth except for the diaphragmatic portions which were studded with tumor nodules up to 3 cm. in diameter. The spleen weighed 160 Gm., and tumor tissue was attached to its outer surface. Cut section revealed no evidence of metastasis. The liver weighed 1,430 Gm. Tumor nodules were present on its outer surface and cut section revealed many nodular areas up to 4 cm. The pancreas was embedded in a mass of tumor tissue. All the coils of the small intestine were surrounded by friable tumor tissue. A uterus, normal in size and shape, was present. Friable tumor tissue filled the cul-de-sac. On the left, the adnexal region was obscured by a tumor mass and the ovary was absent. The right ovary was replaced by a cystic mass 5 cm. in diameter with smooth external surfaces. Cut section revealed numerous cystlike cavities filled with a yellow translucent fluid similar to the left ovarian tumor which was removed surgically. Both tubes were embedded in the neoplastic tissue. The remainder of the organs showed nothing of note.

Microscopic Findings.—The left ovarian mass removed surgically on Oct. 24, 1940, consisted mainly of closely packed lymphatic vessels of varying sizes and shapes. These channels were lined by flattened, one-layered, endothelial cells having a fusiform nucleus (Fig. 1).

In a few small areas, however, the endothelium was several layers thick and consisted of intra- and extraluminal proliferations. Here, the endothelium was swollen and the nuclei more hyperchromatic. A large portion of the tumor mass had undergone necrosis and hemorrhage.

The second surgical specimen, as well as the autopsy material obtained six months later showed loss of the orderly arrangement of the lymphatic channels. All the sections taken through the neoplastic tissue were similar.

Incomplete or poorly formed channels, in which endothelial proliferation had become so marked as to almost completely obscure the lymphatic spaces, was present. The endothelial cells varied in size and shape and contained hyperchromatic nuclei uniformly spherical or ovoid in shape. Masses of these cells extended into the surrounding tissue as buds. In most areas, extraluminal proliferation of endothelium was present and
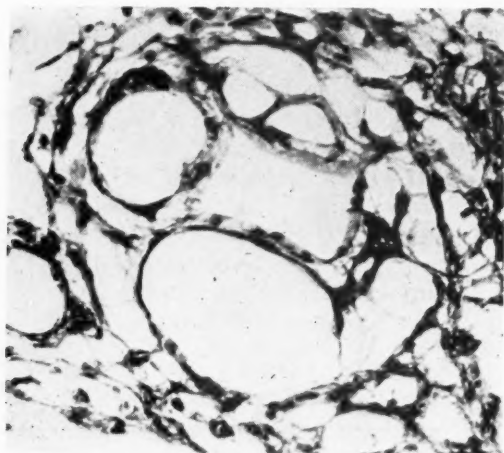

Fig. 1.—Section of the left ovary six months before death, showing closely packed regular lymphatic channels without extra-or intraluminal proliferation.
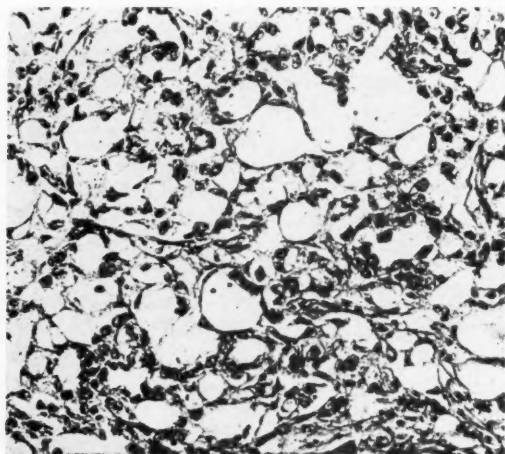

Fig. 2.—Section of the recurrent pelvic tumor mass at autopsy shows irregular lymphatic channels with extra and intraluminal proliferation.

occasionally formed solid sheets (Fig. 2). Large areas of necrosis and hemorrhage were also noted.

The right ovarian mass showed remnants of the normal ovarian stroma (Fig. 3) and neoplastic tissue similar to that described above.

The liver revealed numerous areas of necrosis with or without neoplastic cells. In many areas, there were well-constructed endothelial-

lined lymphatic channels with varying degrees of extraluminal proliferation. The adjacent liver cords were markedly compressed (Fig. 4).

The remainder of the organs showed no evidence of metastasis or any distinctive pathologic changes.

Fig. 3.—Section from the right ovary at autopsy showing normal ovarian stroma and neoplastic lymphangiomatous tissue.
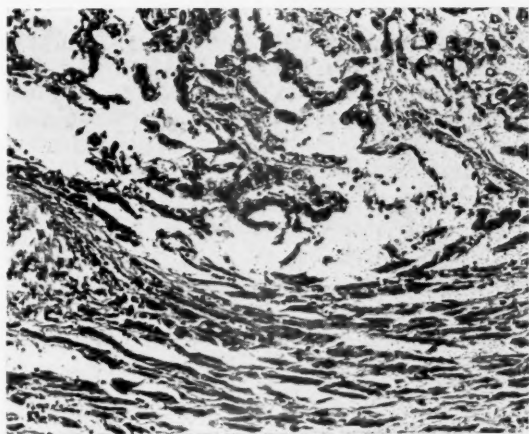

Fig. 4.—Section taken through the liver revealing well-constructed endothelial lined lymphatic channels with varying degrees of endothelial proliferation. The hepatic cords are markedly compressed.

Comment

A diagnosis of a benign lymphangioma was made from the original biopsy, and six months later metastasis and dissemination had occurred. The purely morphologic diagnosis of malignancy in a lymphangioma is very difficult, even in the presence of varying degrees of extra- and intraluminal proliferation. This was practically absent in the first specimen and the tumor consisted of thin-walled dilated spaces, varying in

size and shape. A great deal of necrosis was present, apparently due to the rapid growth of the tumor which makes us believe that the tumor was malignant from the beginning. On pure morphologic grounds, it is difficult to call the first section malignant (Fig. 1). Serial sections were constant in appearance. It is possible that the malignant portions were destroyed by areas of necrosis. In the liver this seemed apparent as numerous large and small areas of necrosis were present with or without tumor cells.

In the post-mortem sections, a profound difference in the morphology was at once apparent. Varying and large amounts of extra- and intra-luminal proliferation had taken place. Instead of the flattened endo-thelium with its dark fusiform nuclei, the endothelium was more swollen and proliferative and the nuclei more vesicular. In some sections, intra-luminal budlike processes could be seen.

The question naturally arises because of the occasional presence of small budlike processes in the lumen that this might not represent tumors similar to those championed by Schiller[6] as "mesonephroma ovarii." In our sections, unlike those of Schiller, the budlike processes represented localized proliferations of the endothelium and could in no sense be interpreted as mesonephric processes.

Recently Kazancigil, Laqueur and Ladewig[7] have described three cases under the caption of papillo-endothelioma ovarii in which there were processes resembling glomerular-like structures. In addition angiomatous and diffuse endotheliomatous areas were apparent. Their first case also contained "granulosa" areas.

Summary

We have presented a case of an apparently morphologically benign lymphangioma of the ovary in which a resection was done. Six months later a local recurrence, peritoneal dissemination, and hepatic metastasis had taken place, and a new growth in the opposite ovary was present. A rather profound morphologic difference was evident between the primary and disseminated neoplasm, consisting of proliferation of the endothelium and changes in the individual cells. However, because of the marked necrosis of the primary together with marked hepatic necrosis present at autopsy make us feel that the tumor was malignant at its inception in spite of the regular benign morphology it presented.

References

1. Kroemer: Handbuch der Gynäkologie, J. Veit, 1908, J. F. Bergman, Weisbaden, p. 332. Quoted by Sidall and Clinton.
2. Fleischer, R.: Monatschr. f. Geburtsh. u. Gynäk. 62: 45, 1923.
3. Sidall, R. S., and Clinton, W. R.: Am. J. Obst. & Gynec. 34: 306, 1937.
4. Schottlaender, J.: Arch. f. Gynäk. 78: 137, 1906.
5. Rössle: Zentralbl. f. Gynäk. 36: 55, 1912.
6. Schiller, W.: Am. J. Cancer 35: 1, 1939.
7. Kazancigil, T. R., Laqueur, W., and Ladewig, P.: Am. J. Cancer 40: 199, 1940.

NORMAL INFANT AND A SYMPUS MONSTER WITH A SHORT CORD IN A TWIN PREGNANCY

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THE most interesting features of the present case are: delivery of twins at term, a normal surviving infant and a sympus monster which died after five minutes; short umbilical cord of the monster, measuring only 5 cm. There were monochorionic membranes, suggesting that the twins were of the single ovum type.

Mrs. J. J. L., white, aged 40 years, weight about 250 pounds, was first seen when admitted to the hospital, in labor, July 14, 1942.

First menstruation at 13, periods regular since. She has 8 living children, all boys, the second pregnancy being twins. There have been no miscarriages. Ages of her children are: 16, 14, 14, 12, 9, 6, 4, 2. All babies were large at birth. Patient stated that her grandfather was one of twins. Her last child was a breech presentation, and was delivered manually.

Last menstruation began Sept. 28, 1941; estimated date of confinement July 8, 1942.

Patient was obese and large framed. Head was normal, eyes clear, teeth good, breasts large, and heart normal. There was no history of any venereal disease. Wassermann was negative. Abdomen was very large, and abdominal muscles flabby. Patient was in the second stage of labor with the right foot presenting. Due to the extremely large size of the abdomen, a diagnosis of twins was made.

Because of the weak abdominal muscles it was thought wise to do a breech extraction. This was done under gas anesthesia and a large male child was delivered with no difficulty. The child was normal and respiration was immediate upon delivery. The placenta did not deliver at this time. Another fetus was felt in the uterus. Internal examination revealed a foot presenting but the other foot could not be felt. A manual delivery was also performed on this child. When the hips were delivered there was some difficulty in delivering the rest of the body. The child was eviscerated. The difficulty in delivering the baby was due to the shortness of the cord, the pull having torn away the umbilical area of the abdominal wall. The intestines were replaced and the wound sutured. The child breathed for about five minutes.

The placenta was delivered by the modified Credé method. Examination showed there was a single placenta with 2 amnions and 1 chorion. The cord of the first child was normal in length while that of the second child was only 5 cm. long. The placental areas of the normal baby and the monster were unequal, the proportion being about 2:1, respectively.

First child: A male which showed no abnormalities. Weight about 9 pounds. Second child: gross examination: The weight was about 4 pounds. The head showed an abnormality of the right lower jaw, the angle of the mandible being absent. The ears had a peculiar shape, were large and lay close to the head. The hands were flexed against

the forearm but could be extended. The fingers could not be fully extended. There were no external genitals. There was an imperforate anus. A small area on the posterior surface of the right hip suggested deviated position of the imperforate anus. The legs were completely fused, and there was a single foot with 6 toes, the foot extending to the left (Fig. 1).

Roentgen Ray Findings.—There were 13 ribs on the left side and 12 ribs on the right. The angle of the mandible on the right side was absent. The vertebral spine showed no well-defined arches; the impression was that of a complete spina bifida. The articular processes of the eighth and ninth thoracic vertebrae could be distinguished on the

Fig. 1.—Note absence of genitals and fusion of lower extremities.

left side. The vertebral bodies were smallest in the region of the eighth and ninth thoracic vertebrae, and the largest in the region of the cervical and sacral vertebrae. There was a slight scoliosis to the left, and a distinct kyphosis in the area of the eighth and ninth thoracic vertebrae (Fig. 2). (Although there was the impression of a complete spina bifida there seemed to be present spinous processes in normal number.) The coccyx extended anterior to the femur. The pelvis appeared to consist of a right and a left os ilium, which were asymmetrical, and a heart-shaped bone between them. There was no proper hip joint but 2 femurs were somehow articulated on each side between the heart-shaped bone and the ilia (Fig. 3). The lower extremities showed a fusion. There were 2 femurs, 2 tibiae, and 1 fibula. The fibula seemed

to be on the medial side of the left tibia. The soft parts allowed one to distinguish a separation between the femurs but not between the tibia. There was one foot, which projected at a right angle from the distal end of the left tibia. One tarsal bone, six metatarsals, and six phalanges were present.
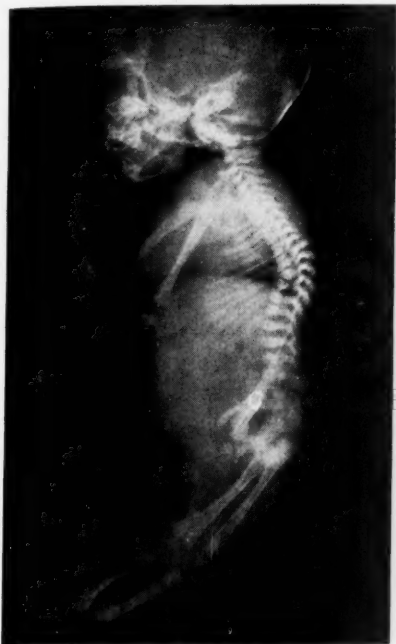

Fig. 2.   Fig. 3.

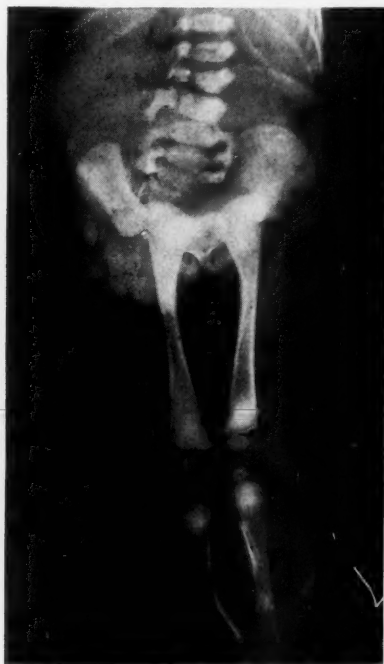Fig. 2.—The coccyx can be seen in front of the femurs. The spinous processes can be counted in this picture.

Fig. 3.—The heart-shaped bone and asymmetrical os ilia can be distinguished easily.

While in the literature there are many records of sympus monsters, the present case is apparently unique in the occurrence of such a monster in a twin pregnancy of which only five instances have been reported.

Reference

Newbill, H. P.:   Am. J. Dis. Child. 62: 1233, 1941.

PREGNANCY AFTER TUBAL STERILIZATION

With the Report of Case Demonstrating Epithelium-Lined Connecting Tube

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JAMES B. BULLITT, A.M., M.D., CHAPEL HILL, N. C.

THIS case is reported because it demonstrated the formation of a patent, epithelium-lined fibrous cord 20 mm. long that connected the separated ends of the divided oviduct after an attempted tubal sterilization. The operation was done in conjunction with a cesarean section and consisted of resection of a wedge from each uterine cornu and plication of a peritoneal fold as described in the case report. Pregnancy later occurred. Following the report the implications of the findings are briefly discussed.

Mrs. H. R. T., white, aged 30 years, two years previously when pregnant and near term, had been operated upon by one of us (G. L. C.) because of the dual indications of disproportion and mitral insufficiency of long standing nearing decompensation.

A low cervical cesarean section was done and a wedge resected from each uterine cornu, care being exercised to include the oviduct in the wedges. The walls of the V left by the removal of the wedges were sutured together, the tubes ligated, and the peritoneal fold from the tubes plicated over the raw area, separating the end of the tube from the cornual wound for a distance of about 2 cm. Number 2 chromic catgut was used.

When readmitted May 5, 1939, the patient was about three months pregnant. The mitral insufficiency was marked but compensated. She was operated upon (G. L. C.) on May 12, 1939, the supravaginal portion of the uterus with its contained pregnancy and both undisturbed, attached Fallopian tubes being removed. Her convalescence was uneventful.

Pathologic Report (S/39/1115) (J. B. B.):

"This specimen consists of a uterus, amputated apparently through the cervix. Its dimensions are: vertical 75 mm.; lateral 96 mm. (near fundus); anteroposterior 65 mm. The posterior surface is strongly convex, the anterior surface flattened (probably from lying on that surface during fixation). The left oviduct is represented by a flattened, irregularly crescentic mass, 20 by 14 mm., firmly plastered against the cornu by a peritoneal covering. When this is dissected free, no lumen can be found grossly or microscopically in the tube nor any opening into the uterus.

"The right oviduct is spirally coiled, forming about one and one-third turns, closely apposed to the uterine wall at the level of the cornu, and (except for about 15 mm. of the distal end) firmly bound to that wall by peritoneum. The fimbriae are shrunken to blunt stubs only one or two mm. in length. Seen through the peritoneal covering the proximal end seems squared off and is located about 20 mm. below the normal point of attachment. When this tube is dissected free and reflected

downward, a slender cord (20 × 2 mm.) is exposed to view. Attached at one end to the side of the proximal end of the oviduct, this cord runs upward to attach at its other end to the uterine wall at about the location of the normal isthmus. Microscopic sections, made at short intervals through the oviduct, show it patent throughout, with essentially
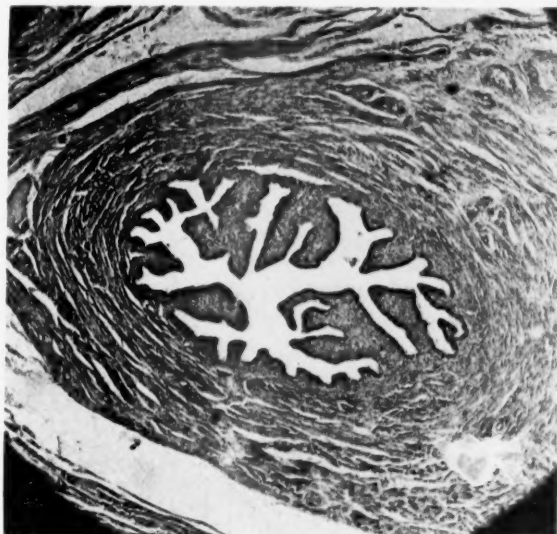

Fig. 1.—Section through remnant of oviduct. ×58.
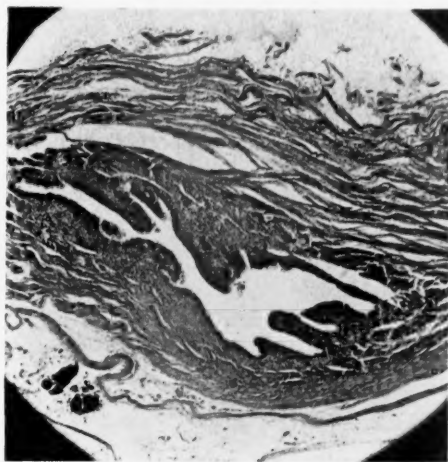

Fig. 2.—Section through canalized fibrous cord connecting this oviduct with the uterine cornu. ×58.

normal architecture except for considerable simplification of the mucosal folds. Sections through the above mentioned connecting cord show it to be a fibrous tissue tube the lumen of which is lined by a thin mucosa, similar to that of the oviduct. Sections of the uterine wall show the continuance of the lumen of the cord to open into the uterine cavity.

This portion of the lumen is somewhat dilated and a little placental tissue projects into it.

"When the uterus is split open laterally an apparently normal fetus (70 mm. long from occiput to coccyx) is seen. The placenta is attached posteriorly, the cord springing from a point about 15 mm. below and to the right of the center of the posterior wall."

Fig. 3.—Section of channel through uterine wall which contains a mass of decidual cells.   ×58.

Fig. 4.—Decidual cells from Fig. 3.   ×160.

This specimen showed very well the urge of epithelium to reconnect. A rather cursory examination of the literature indicates that the process is frequently successful after attempted sterilizations and suggests that better-thought-out obstacles are necessary for its prevention. Operations on the flexible part of the oviduct appear to have about 5 per cent failures. Resections of the cornua appear much more certain of success.

We found references to three patients, however, in whom pregnancy occurred after removal of most of the uterus, and a fourth in whom it occurred after a bilateral salpingectomy accompanied by resection of a wedge from the uterus. Schultze[3] observed pregnancy after total resection of both tubes and amputation of the fundus. Liepman[1a] reported it after supravaginal hysterectomy. McMillan and Dunn[1b] reported two pregnancies in the same patient after supravaginal hysterectomy with excision of all of one tube and ovary and part of the other tube. Lasch[4] reported pregnancy in a woman who had both tubes, wedges from the uterine cornua, and one ovary removed.

An examination of the original operations in the above cases shows the possibilities for recanalization in two of them. In the case reported by McMillan and Dunn, the cut end of the remaining tube had been stitched in with the peritoneum over the stump of the cervix. Cervical canal and tube end may have been in apposition, a suture may have cut through the tube a few days after operation, or a small dead space may have invited epithelization. In the case by Lasch, the remaining ovary had been sutured against the uterine wall, apparently at the site of the removed wedge. A hematoma in the site from which the wedge had been removed would have furnished an excellent opportunity for the epithelium to finish the path from uterus to ovary.

Schultze[3] reported a case that closely parallels ours. This woman had been supposedly sterilized by resection of the isthmic portions of the tubes. Conception took place about fifteen months after operation. On the left side continuity of the tube appeared to have been restored by a fistulous duct. Its epithelium was low, nonsecreting, without fimbriae and partly formed by cells of the decidual type. Musculature was not present. On the right side a fistulous duct was in the making. Both stumps terminated in it but had not yet joined.

The tendency of epithelium to connect with epithelium is well known. What might happen is illustrated in a patient fifty-five years of age upon whom one of us (G. L. C.) operated a few years ago. She might well have had an abdominal pregnancy after a total vaginal hysterectomy, if she had been younger. The wound healed with a small fistulous tract through the vaginal vault, the approximated pubocervical and uterosacral ligaments, broad and round ligaments, forming a patent canal from vagina to peritoneal cavity, that required six months of curetting and cauterizing to obliterate.

As we consider the problem of occluding the oviduct a few basic conclusions appear justified.

1. The ease and rapidity of an operation should seldom, if ever, be deciding factors in determining procedure.

2. The ends of the divided oviduct should have the maximum of spacial separation.

3. In that spacial separation, the greatest opportunity for scar tissue formation and peritonization should be afforded.

4. Careful hemostasis should be observed, as blood clots delay scar tissue healing and give epithelium a chance.

5. Sterilization should preferably be performed on the nonpregnant uterus, because it is far less vascular than the pregnant uterus, and bleeding in the cornual resection is less likely to result in hematoma.

6. A dry technique, silk, cotton, fine linen, should be used on uterus, tubes, broad and round ligaments. The moist technique of catgut with the serum reaction about it over the time required for its absorption delays scar tissue healing and gives the epithelium of the tube a better chance over a longer period of time to form a canal.

References

1. Dipple, H. L.:   Surg., Gynec. & Obst. **71**: 94, 1940.
1a. Liepman, W.:   Arch. f. Gynäk. **51**: 2479, 1927.
1b. McMillan, W. H., and Dunn, R. H.: West Virginia M. J. **16**: 183, 1921.
2. Rubovits, Wm. H., and Kobak, A. J.: AM. J. OBST. & GYNEC. **27**: 12, 1934.
3. Schultze, K. W.:   Zentralbl. f. Gynäk. **61**: 1683, 1937.
4. Lasch, C.:   München. med. Wchnschr. **71**: 55, 1924.

BRENNER TUMOR OF THE OVARY COMPLICATING PREGNANCY

FLOYD S. ROGERS, M.D., WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, George Washington University School of Medicine)

ORTHMANN,[1] in 1899, reported what was probably a Brenner tumor eight years before Brenner[3] in 1907 reported his three cases. Brenner designated these tumors "oophoroma folliculare" and confused them with granulosa cell tumors. It was Robert Myer[4] who, in 1932 described the characteristics of this tumor and offered the generally accepted histogenesis. It is usually agreed that these tumors have their origin from certain cell rests as originally described by Walthard[2] in 1903.

While Brenner tumors are not uncommon, only four have been reported occurring as a complication of pregnancy. Novak and Jones,[6] in 1939, reported 122 cases, three of which were associated with pregnancy. In the first, the patient was four months pregnant when the tumor was removed; while in the second, pregnancy was noted only at the time of hysterectomy and bilateral salpingo-oophorectomy. In the third instance, pregnancy was diagnosed by finding decidual tissue in curettings. In 1940, Siegel[7] reported a single case in which the tumor produced dystocia and was removed at the time of cesarean section. In Danforth's series,[5] reported in 1942, pregnancy was not mentioned. The purpose of this report is to add a fifth instance of Brenner tumor complicating pregnancy.

Case Report

R. R., aged 32 years, para i, gravida ii, whose last menstrual period was May 22, 1942, began uterine bleeding on July 3, 1942. Immediate treatment was instituted, including ephynal acetate, 10 mg., and desiccated thyroid, one-half grain, three times daily, and 5 mg.

of pranone daily. The bleeding was never profuse, but irregular "spotting" continued until Aug. 15, 1942.

Physical examination revealed a well-developed and well-nourished woman, 69.5 inches tall, and weighing 129.25 pounds. The eyes were normal, and the teeth in good condition. The thyroid gland was not palpable. The breasts were tender, but no masses were felt and the nipples were erect. The heart was normal in size, with no abnormal auscultatory findings. The lungs were clear. Abdominal examination revealed a lower right rectus scar, well healed, with no fascial defects. The liver, spleen, and kidneys were not palpable. There was moderate tenderness in the right lower quadrant, but no mass was detected.
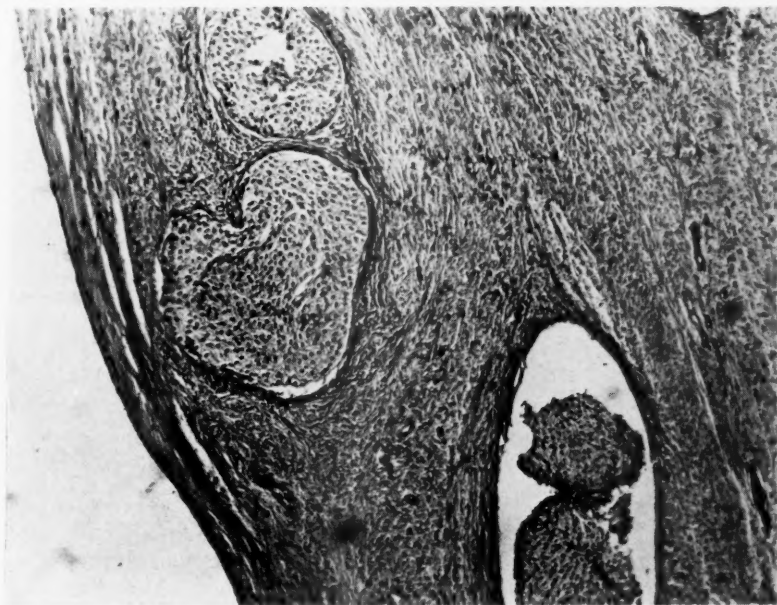

Fig. 1.—Photomicrograph of Brenner tumor wall showing cell rests of Walthard.

Pelvic examination showed a normal distribution of puboperineal hair and the external genitals were normal in configuration. Bartholin's glands and Skene's glands were not palpable. The introitus was parous, with no relaxation of the perineum. The vaginal mucosa was normal. The cervix uteri was firm, movable without pain, and pointed anteriorly. Hegar's sign was positive. Inspection of the cervix revealed no abnormalities. The corpus uteri was retroverted and freely movable, soft, and symmetrically enlarged corresponding to the period of amenorrhea. Anterior and to the right of the uterus was a cystic, nontender, movable mass, approximately 10 cm. in diameter. The left adnexa was not palpable. There was no rectal pathology, and rectovaginal examination confirmed the previous findings. The results of laboratory examinations were as follows: urinalysis, normal; Wassermann reaction, negative; hemoglobin (Sahli), 66 per cent; red blood cells, 3,300,000; and basal metabolic rate, –10.

The patient was admitted to the Emergency Hospital on Aug. 21, 1942, and a laparotomy was performed under avertin-ethylene anes-

thesia. The abdomen was entered through a low midline incision. The right ovary was found to be replaced by a smooth, thin-walled, freely movable cyst, about 15 cm. in its greatest diameter, which displaced the uterus posteriorly. There was also a small thin-walled cyst of the left ovary 3 cm. in diameter. Both Fallopian tubes appeared normal. No corpus luteum was noted. The corpus uteri was soft, retroverted, and symmetrically enlarged, corresponding to the period of amenorrhea. No other pathology was found. A right salpingo-oophorectomy was then performed.

Pathologic Examination.—Gross: The specimen consisted of a right ovary which had been replaced by a large, thin-walled cyst measuring 15 cm. in greatest diameter. It was divided into two distinct saccules. Attached was the Fallopian tube, which was thin-walled and did not appear unusual.

Microscopic Examination.—(Dr. Herbert Traut, Cornell University School of Medicine.) Sections of the Fallopian tube showed a thin wall in which the vessels were injected, and there was an occasional small focus of lymphocytic infiltration. Sections of the ovarian cyst showed a thin fibrous wall in which were numerous islands of closely packed epithelioid cells, resembling the cells found in Brenner tumors. This was a benign growth which evidently had become cystic.

The pathologic diagnosis was cystic degeneration of a Brenner tumor, with chronic salpingitis.

The postoperative course was entirely uneventful. Preoperative therapy was resumed, the patient receiving desiccated thyroid, one-half grain, three times daily, ephynal acetate, 3 mg., twice daily, and 5 mg. of prolution daily. The patient was discharged from the hospital on Sept. 7, 1942, and since that time the pregnancy has progressed normally.

Discussion

A complete survey of the literature on Brenner tumors reveals only four instances which have been associated with pregnancy. To these has been added a fifth case in which the tumor was discovered during pregnancy, and which was removed without disturbance of the normal course. The small cyst of the left ovary probably had its origin from the corpus luteum. The cessation of bleeding at approximately the end of the third month is accounted for by the hormonal action of the placenta, which begins its function at this time.

References

1. Orthmann, E. G.: Monatschr. f. Geburtsh. u. Gynäk. **9:** 771, 1899.
2. Walthard, M.: Ztschr. f. Geburtsh. u. Gynäk. **49:** 233, 1903.
3. Brenner, F.: Frankfurtsh. Ztschr. f. Path. **1:** 150, 1908.
4. Myer, R.: Zentralbl. f. Gynäk. **56:** 770, 1932.
5. Danforth, D. N.: AM. J. OBST. & GYNEC. **43:** 984, 1942.
6. Novak and Jones: AM. J. OBST. & GYNEC. **38:** 872, 1939.
7. Siegel, I.: AM. J. OBST. & GYNEC. **40:** 337, 1940.

CIRCUMCISION OF THE NEWBORN INFANT BY CAUTERIZATION

E. D. Colvin, M.D., and R. A. Bartholomew, M.D., Atlanta, Ga.

CIRCUMCISION of the newborn infant by the cauterization method, described below, has proved to be an ideal procedure, inasmuch as it eliminates loss of blood, prevents infection, minimizes trauma, and secures an excellent cosmetic result, by a technique which is both time-saving and simple.

In addition to mosquito forceps, scissors, an Allis forceps, a small needle and 000 plain catgut, the essential instruments are an electric cautery and a special hemostat for clamping the foreskin. This hemostat can be made by beveling the jaws of an ordinary medium size straight hemostatic forceps at about forty-five degree angles, with an emery wheel, until the jaws meet along a very narrow line when clamped. This insures a minimum of crushed tissue when the clamp is applied and prevents injury to the glans.
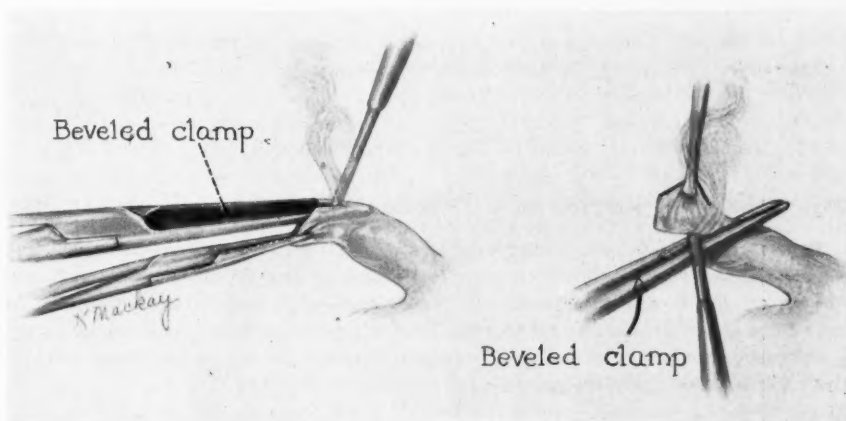

Fig. 1.   Fig. 2.

Fig. 1.—Dorsal slit by cauterization along groove of beveled clamp to permit retraction of foreskin and freeing of adhesions.

Fig. 2.—Removal of redundant foreskin by cauterization along smooth side of beveled clamp. Operation rendered bloodless by cautery and clamp.

After cleansing the genitals with soap and water and draping the field of operation, a curved lubricated mosquito forceps is passed into the opening of the foreskin between the glans and prepuce and repeatedly spread until the glans is freed from the foreskin on its upper surface.

The special forceps is then passed, beveled side up, between the foreskin and upper side of the glans, the foreskin being steadied by traction with a small straight mosquito forceps which grasps it at the tip of the ventral median raphe.

899

By means of the cautery, a dorsal slit is made from the opening of the glans, back for a distance of one-half to one centimeter (Fig. 1), sufficient to permit the foreskin to be pushed back over the corona of the glans, breaking up all adhesions. By cauterizing along the beveled groove of the forceps, the dorsal slit can be made without bleeding or injury to the glans.

The foreskin is then grasped with an Allis forceps at the point where the dorsal slit was begun, approximating the two cauterized surfaces and the foreskin drawn downward. The required length of redundant foreskin is then clamped diagonally from below upward, the beveled surface of the jaws facing the glans. The median ventral raphe serves as a guide in placing the clamp symmetrically on the foreskin. The forceps should grasp more of the foreskin on the dorsal than on the ventral surface.

Since the beveled jaws of this forceps meet along a very narrow line of approximation, there is practically no recognizable line of crushed tissue to be seen after removing the forceps.

The distal redundant foreskin is then removed by cauterizing close to the upper unbeveled side of the forceps (Fig. 2). The crushed cauterized mucocutaneous border is then pushed back over the glans and the mucous membrane and skin are united at 12-3-6 and 9 by fine catgut, or suturing may be omitted if the skin and mucous membrane adhere. The wound may be protected for twenty-four to forty-eight hours by borated vaseline on flat gauze. Healing is very rapid and the ultimate result excellent.

1259 CLIFTON ROAD, N. E.

Boys, Floyd: The Prophylaxis of Peritoneal Adhesions, Surgery 11: 118, 1942.

Based on a careful study and analysis of 188 contributions selected from the world's literature, Boys presents a most exhaustive survey of available information on all the various aspects of peritoneal adhesions. Systematic arrangement of recorded findings in clinical observations and of results reported from experimental work readily convey to the reader a clear picture of the present status of this complex and important surgical problem.

The writer's final summary includes the following statements of facts and suggestions for further study: Up to the present only one prophylaxis has been established against peritoneal adhesions, namely, minimization during operation of all forms of peritoneal damage and avoidance of intraperitoneal infection. The evidence presented from the literature suggests that the use of heparin at present is the most promising supplementary prophylactic measure. It is the only substance proposed which is native to the body, but it does carry the definite risk of hemorrhage. Failure to prove the effectiveness of any measure probably often is due to insufficient laboratory study, which should be continued not for a few months but for years. It will be necessary to investigate other anticoagulants, the absorbable membranes, the sulfonamides and so forth. As preliminary to such studies, acceptable techniques must be developed for standard adhesion production. Clinical evaluation of any measure depends on wider experience and careful examination of findings during a relaparotomy or at post mortem. Reports must be based on large numbers of cases and obviously will require years to accumulate.

HUGO EHRENFEST

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology and Obstetrics

The Hormones in Human Reproduction[1] by George W. Corner is based on the Vanuxem Lectures delivered at Princeton in 1942. These lectures are designed for the laity. Corner has fulfilled the task of making the well-educated lay person understand the very complicated phenomena of reproduction. In doing so he has gone into great detail and built up a foundation based on the lower forms, with gradual transition to human reproduction. In fact the presentation is so thorough that the medical student and the physician will find the lectures valuable and informative, particularly as they are well illustrated by numerous plates and figures, many of which are not readily accessible without minute search of the literature. The author has given a very human touch to his presentation by introducing the history of the various researches; his contacts with the investigators, and his own difficulties, troubles and joys which are so frequent in borderline research. This book is a valuable contribution to this large and interesting field.

R. T. FRANK.

Zondek and Sulman, in the monograph **The Antigonadotropic Factor**[2] have discussed the entire subject of acquired resistance to hormones. This discussion was initiated by Collip's observation that response to the prepituitary factors diminish progressively with continued injections. His interpretation that this was due to "antihormones" has encountered considerable opposition. The authors give an historical review as well as a discussion of previous work by others. The main portion of the monograph deals with the large amount of experimental work which they have performed, some published, some previously unpublished, to clarify the subject. Like many others, they are unable to accept Collip's interpretation. In their work they have tried to obtain similar types of reactions with other hormones. It is evident that the prepituitary secretions elicit this phenomenon more clearly than any of the other hormones, and that it is strictly limited to those hormones which appear to be combined basically with protein. They conclude that the reaction is an immune one, but that it is not demonstrable by any of the usual serologic methods. They sum up the subject in saying that "the gonadotropic factor represents a new type of blood substance which, though closely related to the immune bodies, does not give the in vitro reactions which generally characterize an antibody." While this work is extremely valuable, careful, and reliable, I am unwilling as yet to accept it as final or conclusive.

R. T. FRANK.

The **Atlas of Ovarian Tumors**[3] by Gemma Barzilai gives a systematic and complete survey of ovarian tumors. It forms a diagnostic atlas complemented

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[1] **The Hormones in Human Reproduction.** By George W. Corner. 265 pages. Princeton University Press, Princeton, 1942. (London: Humphrey Milford, Oxford University Press.)

[2] **The Antigonadotropic Factor.** With Consideration of the Antihormone Problem. By Bernhard Zondek and Felix Sulman, Hebrew University, Jerusalem. 185 Pages. The Williams & Wilkins Company, Baltimore, 1942.

[3] **Atlas of Ovarian Tumors.** By Gemma Barzilai, M.D. Prefaced by Fred W. Stewart, M.D., Pathologist, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City. 261, pages. Grune and Stratton, New York, 1943.

by a short, lucid, and very original text. The macroscopic appearance of tumors are not illustrated but the entire clinical aspects, such as frequency, age incidence, gross pathology, clinical signs and symptoms, malignancy, and benignancy, and proper method of treatment are contained in the text, which, to some degree, is based on lectures given by the author to her students at the University of Padua and considerably influenced by the Vienna school of pathology, particularly that of Schiller.

The classification of ovarian tumors is based on developmental origins as far as is possible. It is in the main original and yet neither bizarre nor too heterodox. In brief, it includes neoplasms developed from the follicle, the mesenchymal core of the ovary, those from totipotent cells, then from structures of extrafollicular portions of the ovary. Other tumors are derived from structures adjacent to the ovary in the adult stage but in close connection with the embryonal ovary (Müllerian, Wolffian and enteric tissues); finally, secondary ovarian growths. On the whole, the classification is clear and can actually be followed out in the pathology. Of special interest is the "endosalpingioma" which the author ascribes to Müllerian derivatives of tubal origin. Such tumors have previously been classed under many different names, perhaps the most striking of which is the papillary cystadenoma. Twenty per cent of ovarian neoplasms, according to Barzilai, fall into this group. They are the tumors which defy cytologic classification of malignant or benign, and have proved a puzzle to the gynecologic pathologist. Another group is the mesenophroma which contains specific structural units of embryonal glomerulus, the tumor cells being of endothelial type.

The fifty-eight plates, many in colors, are of exceptional excellency. The majority of the black and white microphotographs, well chosen, striking specimens, magnificently reproduced.

The Atlas should prove of great value to gynecologic pathologists as well as to pathologists whose material is scantier and who will find a means of ready reference which can only be replaced by a large slide collection acquired over many years. The marginal headings add greatly to the facility of reference. Although the literature is frequently alluded to throughout, there is no bibliography. It is rare today to see a book so well illustrated as this Atlas.

R. T. FRANK.

The last ten or twenty years have brought a surprising number of discoveries in what appeared to have been the thoroughly studied field of the morphology of ovarian tumors. This has stimulated a general review of the pathologic material in the ovarian tumor collections of many institutions and a reappraisal of related clinical problems. The studies of these years are now culminating in more definitive works on the subject of ovarian neoplasms.

Ovarian Tumors[4] by Samuel H. Geist, Attending Gynecologist at the Mt. Sinai Hospital is such a work. It is based on the study of over 1,100 cases of benign and malignant ovarian tumors and a thorough review of the recent and much of the early literature. With this material the author presents a comprehensive picture of the subject as a whole with detailed consideration of the clinical and pathologic characteristics of each of the many special types of ovarian tumors.

The practical aspects of the subject have been stressed. Each variety of ovarian tumor is presented with excellent illustrations of gross and microscopic preparations. The latter will be of special service to the pathologist in aiding him to classify his own material. Correlated description of the clinical aspects of each tumor has resulted in this being much more than a mere pathologic treatise. The bibliography is sufficiently ample to make this book a valuable work of reference for the preparation of manuscripts for publication.

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[4]**Ovarian Tumors.** By Samuel H. Geist, M.D., Attending Gynecologist, Mount Sinai Hospital; Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University. With 312 Illustrations. 527 pages. Paul B. Hoeber, Inc., New York, 1942.

No present classification of ovarian tumors can be universally satisfactory and Geist has accepted in advance the probability of criticism by offering a classification of his own. The classification, to this reviewer, seems so expanded as to present an unusually formidable appearance. In addition, the Geist plan of subdivision continues to utilize some unproved hypotheses of histogenesis to form the basis of major subdivisions. The distinction between ''surface'' and ''subsurface'' origin is an example in point, since the origin of pseudomucinous tumors, at least, from the surface endothelium is not finally accepted. The classification also seems unduly encumbered with varieties of sarcomas, peritheliomas and other tumors whose very existence is now in considerable doubt. These are, however, objections based on viewpoint and are not errors in fact. The book remains one of the best available sources of information on ovarian tumors and one which is certain to be of value both to the gynecologic surgeon and pathologist.

HOWARD C. TAYLOR, JR.

The fourth edition of Curtis' **Textbook of Gynecology**[5] has appeared within four years, bespeaking the popular approval of this work. The new edition shows extreme care in revision, with incorporation of all the newer discoveries which have occurred during this period.

The already excellent chapter on anatomy has been enlarged by the addition of a number of beautiful dissections, including those of the pelvic autonomic nervous system. The entire volume has almost one hundred additional illustrations. All of the gross illustrations are from the artistic pen of Tom Jones. Every chapter has been carefully gone over and revised. The one dealing with the present status of endocrine therapy is short, conservative, sane, and to the point. Although the American trend for treatment of carcinoma of the cervix by means of radium is approved and accentuated, an excellently illustrated description of a modified radical operation for abdominal removal of carcinoma of the uterus is pictured. The treatment of gonorrhea has been entirely revised in accordance with the discovery that the sulfa drugs have proved so sovereign in the cure of this disease in the female. I am in full accord with the advice to discard or limit the local treatment of gonorrhea to the minimum. I likewise agree with Curtis' opinion which ''indicates that operation for eradication of infection is rarely necessary . . .'' but disagree heartily with the opinion that ''surgery, when resorted to, should be directed to reconstruction of tissues laid waste by disease rather than to removal of organs for the purpose of stamping out infection.'' In my experience, if operation is indicated, except when it involves the mere drainage of purulent accumulations, a very radical removal cures the patient, while less radical measures rarely improve the symptoms.

I would suggest that in mentioning the value of the sedimentation test for the diagnosis of ectopic pregnancy, some indication of what changes occur in that disease should be added, and that a reference to it should also be put in the index. On the whole, I know of no book in the English language which covers the subject of gynecology more completely and satisfactorily within short compass than that of Curtis.

R. T. FRANK.

Essentials of Gynecology by Cooke[6] is a students' textbook covering the entire subject. The anatomy is well dealt with, chiefly because excellent reproductions of Peham and Amreich's colored plates have been used as illustrations. These illustrations are at present difficult to obtain and therefore have a great value. The author

covers the entire subject of gynecologic as well as obstetric conditions frequently encountered by the gynecologist. He is evidently an experienced teacher and therefore knows how to present the facts simply. The concluding chapter on the more commonly used operations for gynecology is an epitome of the various steps useful for student review. The illustrations are excellent, particularly the careful line drawings.

There are numerous statements which will not be agreed to generally. For example: The exaggerated importance ascribed to dysmenorrhea due to retroflexion as well as the treatment of this syndrome by viburnum prunifolium or by thyroid extract. That the removal of a hypertrophied cervix in prolapse plays a role by lessening the weight of the uterus, is far from convincing. In dealing with gonorrhea, the subject is somewhat beclouded by taking up the various localization points separately in detail.

R. T. FRANK.

The eleventh volume of the **Transactions of the Pacific Coast Society of Obstetrics and Gynecology**[7] reflects the splendid use of clinical material and the fine scientific work being done on the west coast. The volume opens with a discussion on the ''Specific Interacting Substances of Eggs and Sperm'' by the guest speaker, Dr. Albert Tyler at the annual meeting in 1941. Dr. Tyler concludes this very interesting paper by stating that certain specific substances, extractable from eggs and sperms from various animals, are complementary proteins and interact as in serologic reactions between antigens and antibodies. Concerned with the initial stages of fertilization process, their specificity of action can count in part, at least, for the degree of species and tissue specificity exhibited in fertilization.

The subject matter of a Symposium on Cancer and one on Infertility covers both the research and practical aspects of these two topics. There are several other excellent presentations. The address of the President, which closes the transactions, is an historical sketch on the Development of the Various Oxytocic Drugs.

This volume marks the end of the first ten years of this organization and from a perusal of the transactions it would seem that such a regional organization must have played a great part in the development of ideals of this speciality in the western part of the United States.

PHILIP F. WILLIAMS.

De Souza Rudge, in a bulky monograph, describes the **Treatment of Urogenital Fistulae by the Flap-Splitting Method.** The preface is written by De Moraes Barros, the chief of the service, which is the Gynecological Clinic of the Medical Faculty of the University of San Paulo, Brazil.[8] In the course of twenty years, 122 patients with fistulas have been operated upon. One hundred and three of the fistulas were due to obstetric causes (fifty ascribable to necrosis) and only eleven were of gynecologic origin (postoperative). A short, detailed description of each of the cases is appended.

Spinal anesthesia was used throughout. Stress is laid on full exposure of the fistula, if necessary by liberal Schuchardt incisions. The vaginal flaps are mobilized by a T-shaped incision and the fistulous edges approximated by two layers of double zero catgut, followed by closure of the vaginal defect. Of the 104 cases described, 75 per cent were cured. The casuistic includes every conceivable type of fistula. Colored plates illustrate the operative procedure.

R. T. FRANK.

[7]**Transactions of the Pacific Coast Society of Obstetrics and Gynecology 1941.** Volume XI. 177 pages. Western Journal of Surgery Publishing Co., Portland, Oregon, 1942.

[8]**Tratamento Das Fístulas Uro-Genitais pela plástica Do Desdobramento.** By W. De Souza Rudge, Livre-Docente de Clínica Ginecológica da Faculdade de Medicina da Universidade de S. Paulo. Prefácio do Prof. N. De Moraes Barros, Catedrático de Clínica Ginecológica da Faculdade de Medicina da Universidade de S. Paulo. 225 Pages. Livraria Ateneu, José Bernardes, Rio de Janeiro, 1942.

Salerno's short monograph submitted as a doctorate thesis, at the University of Buenos Aires, deals with **Hematosalpinx of Non-pregnancy Origin.**[9] Bazy, in 1910, gave the syndrome the name of "Paquisalpingitis Hemorrhagica." According to Salerno, Bazy described three cases, and Paucot and Bédrine another case. He has found no other references to this syndrome in the world literature. He personally observed four cases. According to the author, the pathology is based on chronic, inflammatory lesions of the genitals, affecting particularly the local vascular system.

<div align="right">R. T. FRANK.</div>

The Lying-in Hospital of New York was founded in 1799. It has been in continuous existence but at intervals has seen radical reorganization. The second edition of a **Handbook of the Lying-in Hospital**[10] which is now the Woman's Clinic of the New York Hospital, should prove of interest to many, in addition to obstetricians and gynecologists, as it contains in brief outline the organization, practice, therapy, and general diagnostic methods in use at this hospital, including the duties of the resident staff, the students, and the nurses. It covers the routine and the techniques. It was primarily designed to help complete co-ordination between doctors and nursing staff, applying both to obstetric and gynecologic patients. It covers such subjects as the entire survey of a normal woman in labor, from her entrance into the hospital until the completion of her stay, and similarly treats the gynecologic patient. In its pages will be found such diverse subjects as the blood bank, the routine for scrubbing up, the method of collecting various bloods and urines for special tests, sample menus, the management of special cases, and the details of every procedure that is used, for example, details of postoperative catheterization. While no attempt at dogmatism is made, the methods that are at present in use in the Lying-in Hospital are given. The booklet is short, concise, and contains a huge amount of information, readily accessible and clearly stated.

<div align="right">R. T. FRANK.</div>

In this study, **Group Differences in Urban Fertility**[11] which has been derived from a national health survey, certain conclusions are drawn regarding the subject of population increase in various areas. One notes that the fertility rates of white, foreign married women are now a little higher than those of native, white, married women of urban areas, and that urban Negro marriages are more and more characterized by low fertility levels. The class differences are shown to have marked effect on both the fertility and reproduction rates. A high pregnancy wastage is noted among urban, white women of all classes. There is a thorough consideration of the problems relating to fertility and population policies but no formula for encouraging more babies is brought out. It would seem from the philosophic discussion presented that a social program in its broadest sense would be necessary to increase reproduction on a voluntary basis. This book should be of interest to those who are concerned with the various problems of population and reproduction.

<div align="right">PHILIP F. WILLIAMS.</div>

The **Recent Advances in Obstetrics and Gynaecology**[12] by Bourne and Williams has appeared after an interval of three years. As the authors suggest in their preface, it does not exactly include only "recent advances" but appears to

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[9]**La Paquisalpingitis Hemorragica.** Tesis de Doctorado. By Enrique V. Salerno. 73 pages. Cayetano Vergara, Buenos Aires, 1942.

[10]**Handbook of the Lying-in Hospital.** 158 Pages. Woman's Clinic of the New York Hospital, New York, 1942.

[11]**Group Differences in Urban Fertility.** A Study Derived from the National Health Survey. By Clyde V. Kiser, Member Technical Staff, Milbank Memorial Fund. 284 Pages. The Williams & Wilkins Company, Baltimore, 1942.

[12]**Recent Advances in Obstetrics and Gynaecology.** By Aleck W. Bourne, M.A., M.B., B.Ch. (Camb.), F.R.C.S. (Eng.), F.R.C.O.G., Obstetric Surgeon to St. Mary's Hospital, etc., and Leslie H. Williams, M.D., M.S. (Lond.), F.R.C.S. (Eng.), F.R.C.O.G., Obstetric Surgeon to Out-Patients, St. Mary's Hospital, etc. Fifth Edition, with 72 illustrations. 363 pages. The Blakiston Company, Philadelphia, 1942.

resemble a cumulative year book. The present edition includes a new chapter on postnatal care as well as some revision of chapters dealing with the sex hormones. It likewise includes our knowledge of the sulfa drugs and their use in therapy.

Judging by the bibliography, many important new articles have not been included. The authors are somewhat overoptimistic about the effect of estrogens followed by progestine in the cure of secondary amenorrhea. That the book fills a definite want is apparent from the fact that it has gone through five editions since 1926.

R. T. FRANK.

Miscellaneous

The bound brochure entitled **The Author, Publisher, Printer Complex**[13] by Robert S. Gill was evidently written by a veteran in the publishing business. It should prove of utmost interest, particularly to budding authors, but can be read with pleasure and profit by the most experienced and blasé writer. It is written in a pleasant though not flippant vein by someone who is evidently disabused by his numerous contacts with authors some of whom must have shown the prima donna complex.

The relation of author, publisher, and printer is defined and this covers much of the business of bookmaking. The author is the supplier; the printer is the manufacturer; the publisher is the merchandizer. Each has his rights and duties. The cost of printing includes only about one-fourth to one-fifth of the price. Binding plays but a small role in the entire expense, and therefore in this country books are solidly bound rather than in paper covers. The publisher in dealing with authors, knows that "The well-known name is in itself an advertisement" but that does not mean that an unknown cannot make himself heard if he has something worth while to say. Sometimes, to bridge the gap, a well-known figure is selected to write a foreword, but it should be remembered that "There are those so much sought after as introducers, and so amiable, that their forewords are worth precisely nothing at all."

The subject of royalty can prove a stumbling block between an unreasonable author or a grasping publisher. It should be remembered that "a fair royalty is not one that emerges from a compromise between the publisher's cupidity and the author's insistence on his rights, but one that it is reasonable to suppose the customer is willing to pay." The author may prefer to be a co-publisher by making contribution to the cost of publishing. If so, his royalty naturally is increased because he is taking a share of the expense and of the risk.

In the concluding chapter, Gill speaks of incomplete manuscripts which add greatly to the tribulations of the publisher and printer as well as adding to the costs. He shows what "bad" copy consists of and what "fair" copy is. He details the various methods of improving copy, making corrections, printer's changes, etc. Then he deals with the ends and oddments such as the preliminary pages and the index, and concludes this very informative pamphlet with guidance about illustrations.

R. T. FRANK.

The increasing longevity of our population emphasizes the medical care of old people. Since the number in the higher age brackets has become constantly greater in recent years, and doubtless will continue to do so in the future, such a book as **Internal Medicine in Old Age**[14] by Dr. Mueller-Deham and Dr. Rabson should be

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[13]**The Author, Publisher, Printer Complex.** By Robert S. Gill. 76 pages. The Williams & Wilkins Company, Baltimore, 1940. Reprinted in 1941.

[14]**Internal Medicine in Old Age.** By Albert Mueller-Deham, M.D., Associate Visiting Physician, Welfare Hospital for Chronic Disease, etc., and S. Milton Rabson, M.D., Assistant Professor of Pathology, New York Post-Graduate Medical School, Columbia University, etc. 396 pages. The Williams & Wilkins Company, Baltimore, 1942.

welcome not only to specialists in internal medicine but to all those whose practice will bring them in contact with the older or senile patient. The discussion in the text is limited to internal medicine in old age and embraces the status, problems, difficulties, and other broad components of geriatric medicine. Of particular value to the gynecologist is the section dealing with the urogenital system in the aged female.

PHILIP F. WILLIAMS

The Connecticut Medical Society has performed a useful task in compiling the series of articles, **The Essentials of Emergency Treatment,**[15] dealing with the problems of emergency practice which may arise during a period of war. The subject matter describes the types of injuries which may follow the effects, directly or indirectly, of any type of bombardment or destruction. After such general topics as "Organization of Emergency Medical Associations in the Community," there are articles on shock, chemotherapy, blood transfusions, and emergency field treatment. Regional injuries are then taken up seriatim. These are well worked up and concisely presented, and a reading of this book should prepare the civilian professional services very well for the part they might be called upon to play at any time. It is of some interest that no mention has been made of emergency obstetric complications.

PHILIP F. WILLIAMS.

The fourteenth semicentennial edition of Osler's **Principles and Practice of Medicine,**[16] originally written by Dr. Osler, is presented by Dr. Henry A. Christian, the present editor. This classic text has guided many generations of medical students. The influence of the fine men who have previously edited the book have mellowed its teachings.

In the present edition, in which much new material has been added, the text shows a considerable re-arrangement. Osler's *Practice in Medicine* belongs on the handy book shelf of every obstetrician, since constantly through the pages reference is made to the influence of pregnancy on one disease or another, or the complicating effect of various medical conditions on the reproductive functions.

PHILIP F. WILLIAMS.

This **Manual of Radiotherapy** is an outline of the basic x-ray and radium techniques employed in the radiotherapy department of the Presbyterian Hospital in New York.[17] Its purpose, as stated both in the foreword and in the introduction, is for guidance of the departmental residents and for students at the beginning of their work in this specialty. The author stresses quite correctly in the introduction that no hard and fast rules can be made for any individual situation, that variations in lesions and in the general condition of the patient will often call for modification of basic technique.

Practically all pathologic conditions both benign and malignant that are amenable to radiotherapy are discussed. There is a brief description of the signs, symptoms, histopathology and in some instances of the differential diagnosis of the various topics; this is followed by an outline of the basic radiotherapeutic technique. The

[15]**The Essentials of Emergency Treatment.** Edited by Herbert Thoms. 144 pages. Published by The Connecticut State Medical Journal, New Haven. Printed by The Whaples-Bullis Co., Inc., New Haven, 1942.

[16]**The Principles and Practice of Medicine.** Originally written by Sir William Osler, Bart, M.D., F.R.C.P., F.R.S. Designed for the Use of Practitioners and Students of Medicine. By Henry A. Christian, A.M., M.D., LL.D., Hon. Sc.D., Hon. F.R.C.P. (Can.), F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. Fourteenth, Semicentennial (1892-1942) Edition. 1,475 pages. D. Appleton-Century Company, New York, 1942.

[17]**A Manual of Radiotherapy.** By Murray M. Friedman, M.D., Assistant Professor of Radiology, College of Physicians and Surgeons, Columbia University; Assistant Radiologist, Presbyterian Hospital, New York, N. Y. With a foreword by Maurice Lenz, M.D. 86 pages. Edwards Bros., Ann Arbor, Mich.

last 20 pages are devoted to physical charts and methods which were made by Paterson and Parker in Manchester, England, and by Edith Quimby and her co-workers in New York. These tables and charts are invaluable to the radiotherapist who outlines treatment for each individual case in contradistinction to those who treat by rule of thumb or on empirical basis.

The basic techniques described agree in the main with those conventionally used in modern radiotherapy clinics. They establish a ready reference for the sound treatment of any benign or neoplastic lesion. Naturally variations in equipment and individual needs will require adjustments. For instance the radium therapy is done with element needles and tubes. Many clinics would use radon implants where the element is not available or for greater flexibility, as the case may be in bladder cancers. Exception is taken to the statement on page 45, where the author says "Diagnostic curettage is desirable when radium treatment is planned but is not essential in x-ray therapy." It is a universal teaching that diagnostic curettage should precede all forms of radiotherapy in uterine bleeding. Arrangement of the table of contents alphabetically would facilitate the use of this manual.

WILLIAM HARRIS.

Society Transaction

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 24, 1942

The following papers were reported:

Case Report: Multiple Pregnancy, Pyelonephritis, and Septicemia. Joseph Harris, M.D.

Cerebral Complications Occurring in the Toxemias of Pregnancy. John Parks, M.D., and Jed W. Pearson, Jr., M.D. (For original article, see page 774.)

Psychiatric Observations on Forty Cases of Induced Abortion. Beatrice B. Berle, M.D. (by invitation).

Department of Reviews and Abstracts

Selected Abstracts

Cancer

Morton, Daniel G.: Early Diagnosis and Proper Treatment of Cervical Cancer, J. A. M. A. 118: 271, 1942.

The figures from the University of California Hospital show that two-thirds of the women seeking treatment for cervical cancer had advanced growths. Late diagnosis, then, is the chief limiting factor in achieving significant improvement in results.

The average duration of symptoms in this group of cases was 8.7 months. The earlier the symptoms were recognized the higher was the percentage of cures. Periodic examination is also a possible factor in early diagnosis. The ability to recognize cancer in its early stages is not always an easy one. Schiller's test and the colposcope are aids in the early diagnosis of early carcinoma. The most important procedure is in obtaining a biopsy.

High voltage roentgen ray and radium therapy is the treatment in the vast majority of cases.

WILLIAM BERMAN.

Hoffman, Paul E.: Ureteral Obstruction Following Irradiation of Cancer of the Cervix, West. J. Surg. 50: 69, 1942.

Ureteral obstruction with consequent ureteral dilation, hydronephrosis, loss of renal function and a terminal uremia is the most frequent cause of death in patients suffering from Stage III and IV cervical cancer. Intensive ureteral dilatation of the affected ureter as a means of alleviating this condition has proved disappointing, and other methods will have to be devised.

These are the author's conclusions based on a study of 97 patients with cervical cancer.

HUGO EHRENFEST.

Walter, Robert I., Bachman, Arnold L., and Harris, William: The Treatment of Carcinoma of the Ovary. Improvement of Results With Postoperative Radiotherapy, Am. J. Roentgenol. 45: 403, 1941.

A clinical classification of ovarian carcinoma according to stage of progression is presented, and the necessity for its use in evaluating therapeutic results is stressed. This material consists of 124 cases of ovarian carcinoma which are reviewed with particular reference to therapeutic results. The primary operative mortality was 9.8 per cent. Sixty-three patients with ovarian carcinoma were treated by surgery alone. Of these, four, or 6.3 per cent, survived five years. Sixty-one patients were treated by surgery plus postoperative radiotherapy. Thirty-one patients received moderately large amounts of radiation (considered as ''adequate'' in this

series) and seven (29 per cent) were alive five years. Twenty received "inadequate" radiation dosage and two (10 per cent) survived five years.

The major factor in prognosis and determination of type of therapy to be employed is the clinical stage of progression of disease. Morphologic classification and histologic grading appear to be of minor importance. Maximal dosage of radiation therapy should be employed whenever possible.

J. P. GREENHILL.

Cosbie, W. G.: Carcinoma of the Vulva, Canad. M. A. J. **43:** 439, 1940.

Carcinoma of the vulva is a disease of later life. Neglect of symptoms results in an unnecessarily high percentage of advanced cases. In the author's opinion radical vulvectomy offers a hopeful prognosis. Simple vulvectomy and indifferent gland excision have no place in the cure of carcinoma of the vulva. Radiotherapy is of value in the treatment of elderly patients.

J. P. GREENHILL.

Berven, Elis G. E.: 177 Cases of Primary Vulva Carcinoma, Acta Radiol. **22:** 99, 1941.

Berven reviews the treatment of carcinoma of the vulva and reports the results of operation. (According to comprehensive collective statistics the percentages of five-year cures are 4 to 10 per cent, some hospitals report five-year cures in 17 per cent or 35 per cent of the cases studied, and Taussig reports a five-year cure of 65 per cent.) The percentage of five-year cures attained with radiologic treatment is 11.9 per cent. At the Radiumhemmet a five-year cure of 13 per cent was attained.

Since 1922 carcinomas of the vulva are treated at the Radiumhemmet by electro-coagulation of the tumor of the vulva combined with teleradium treatment of the glandular regions and eventual dissection en bloc of the glands in cases amenable to surgical intervention. Among 177 cases of primary carcinoma of the vulva 65 cases, or 36.7 per cent, were alive five years or more free of symptoms. If there is no clinical evidence of metastases (Stage I), it is advisable to treat the glandular regions by teleradium and to perform dissection not before clinical evidence of metastases has been noted. In this stage, 59.3 per cent of the cases were free of symptoms for a period covering five years. Cases presenting clinical metastases (Stage II) should be treated by teleradium combined with subsequent dissection, if the metastases do not disappear. In this stage freedom of symptoms was attained in 22.9 per cent of the cases for a period covering five years. Cases presenting inoperable metastases (Stage III), should only be treated by teleradium. In such advanced stages dissection does not seem to be appropriate. In this stage freedom of symptoms was attained in 3.8 per cent of the cases for a period covering five years. The percentage of postoperative mortality with electrocoagulation and surgical removal of the glands is only 8.5 per cent.

J. P. GREENHILL.

Newcomer, Elizabeth: Comments on Treatment and Sequelae of Carcinoma of Uterus, Am. J. Roentgenol. **45:** 651, 1941.

According to Newcomer, fistulas are seldom due to faulty methods of irradiation but to the extension of the disease. Constriction of the ureters, ureteral dilatation and hydronephrosis are also generally due to extension. A dull, nagging pain in the hips, groin or radiating down to the thigh or leg may be caused by ureteral obstruction. Cystoscopy and visualization of the ureters are indicated in such cases. Similar symptoms are caused by extension of the disease to the lumbar and sacral nerves and to the uterosacral ligaments. Masses may form on the side walls

of the pelvis by extension through the parametrium and broad ligaments, causing excruciating pain. Pressure on the veins of the lower extremities may result in edema of the lower limbs and external genitals. Invasion of the rectum may result in stenosis, ulceration, intestinal obstruction, and fistulas. If lower abdominal pain follows radium application, patency of the cervical canal must be established. Roentgen therapy should precede radium therapy. It reduces infection and the size of the tumor, makes the application of radium safer, renders possible the giving of a heavier dose of radium and distributes it more evenly throughout the tumor. Radium should be given in both the uterine and the cervical canals in doses short of tolerance by the surrounding tissues. As large a dose of radium as can be safely tolerated should be applied to the vault of the vagina by means of the bomb, colpostat or interstitial irradiation in selected cases.

J. P. GREENHILL.

Baatz, H.: Influence of Castration on Growth of Carcinoma, Zentralbl. f. Gynäk. **65: 472, 1941.**

Investigating the hypothesis that castration has an influence on the growth of carcinoma, Baatz implanted adenocarcinomatous tissue in castrated female mice at operation and at intervals of eight to ninety days. Two other groups were first implanted and castrated seven and sixteen days later. Another group in which spontaneous carcinoma was found was castrated. From his study of the tissues the author concludes that in mice, at least, prejuvenile castration would seem to prevent establishment or inhibit growth of mammary carcinoma. On the contrary prophylactic castration in older animals apparently encouraged more rapid growth of the implanted tumor. Castration during the age of greatest ovarian activity, which Baatz terms late castration, also led to increased tumor growth. The author feels that though castration per se will not solve the problem of mammary carcinoma, the solution lies somewhere in the endocrine mileu.

R. J. WEISSMAN.

Hinselmann, H.: Active Proliferation of Capillaries in Early Portio Carcinoma as a New Means of Differential Diagnosis, Zentralbl. f. Gynäk. **64: 1810, 1940.**

Hinselmann, in attempting to improve his diagnostic accuracy through colposcopy, now makes a special study of the blood vessels to be seen in suspicious areas by sodium vapor monochromatic illumination. An 18× magnification is used instead of the usual 12×. Normal tissue appears an even gray and the small venules can barely be seen. The areas of early carcinoma are whitish, and the small vessels, arterioles as well as venules, may be seen and studied. They appear black, enlarged and quite erratic in their course and distribution. Hinselmann now feels that he can make a positive diagnosis of carcinoma of areas which he would previously have labeled suspicious of carcinoma.

R. J. WEISSMAN.

Hoppe, W.: The Value of Radical Operation as an Elective Treatment of Carcinoma of the Cervix, Zentralbl. f. Gynäk. **64: 1126, 1940.**

The author shows a five-year survival of 71 per cent of 62 cases of carcinoma of the cervix operated upon from 1930 to 1933. Primary mortality was 8 per cent. The increase of 15 per cent over previous survival figures is attributed to prophylactic postoperative radiation. In women under 40, the five-year survivals are 28 per cent higher in operated than in radiated cases. The author's figures are broken down as follows:

<div style="text-align:center">

Grade I   43 cases—survival 77%
Borderline 10 cases—survival 80%
Grade II   9 cases—survival 33%

</div>

Of those patients showing carcinomatous glands, 43 per cent survived as compared to 80 per cent in which the glands were not involved.

Points in treatment: (1) Patients showing a strong positive Ruge-Phillipp virulence response were not operated upon. (2) All patients since 1936 received prontosil. (3) All young women received endocrine treatment the first few postoperative days. (4) Since 1939 roentgen radiation has been given three weeks postoperatively and at the same time 1,000 mg. hr. radium is applied. The vulval and gluteal fields are not neglected. The tendency appears to be toward higher dosage and application closer to the time of operation.

R. J. WEISSMAN.

Klüver, R.: Latent Portio Carcinoma in Sisters, Zentralbl. f. Gynäk. 64: 1219, 1940.

The author gives added evidence of the life-saving value of routine colposcopy. A 44-year-old woman was operated upon for myomas of the uterus and atypical portio epithelium. Nothing in the symptomatology was indicative of the presence of carcinoma. The menses had recently been somewhat prolonged and the patient complained of monthly backache, a symptom of years' duration. Several colposcopic examinations revealed extension of the leucoplakia deep into the cervical canal. Microscopic sections of the operative specimen revealed carcinoma. At the patient's request her sister, aged 43 years, was then examined. Here the colposcope revealed erosion on the anterior cervical lip and an extensive area of soft whitish leucoplakia extending well into the cervical canal. Portio amputation was done and microscopic examination confirmed the presence of cancer. There was no evidence of extension in either case.

R. J. WEISSMAN.

Winterton, W. R.: A Comparison of Results of Surgery and Radiotherapy in Carcinoma of the Cervix Uteri, Brit. M. J. 1: 195, 1941.

A series of 179 cases of carcinoma of the cervix seen in patients from 31 to 80 years of age (average age equaled 53.5 years) is presented. Of these cases 152 were squamous celled carcinoma and 7 were adenocarcinoma. All cases deemed operable, except 2, were given the benefits of surgery; the rest were referred to radiotherapy. Of the 64 patients treated with surgery, 5 also had postoperative x-radiation. Of the 115 referred to radiotherapy, 87 were treated with radium (Paris method) and x-rays; 14 by radium (Stockholm method) alone; and 11 were untreated.

The surgical cases were classified in 2 groups; (1) with gland metastasis (2) without gland metastasis. The radiotherapy cases were grouped according to the League of Nations Classification.

The results, based on a five-year survival criterion, show that of the series, 49 survived, giving an absolute survival rate of 27 per cent or a relative survival rate, deducting cases that refused treatment or died of other causes, of 30 per cent.

The author points out the difficulties of accurately comparing the results obtained with surgery and radiotherapy but concludes that in all technically operable cases a higher percentage of five-year survivals has been obtained by radiotherapy than by surgery. There is also a much lower treatment mortality with the former. With technically inoperable cases, a few five-year survivals have been obtained.

FRED L. ADAIR AND W. H. PHILLIPS.

Item

American Board of Obstetrics and Gynecology, Inc.

The general oral and pathological examinations (Part II) for all candidates will be conducted at Pittsburgh, Pennsylvania, by the entire Board from Thursday, May 20, through Tuesday, May 25, 1943. The Hotel Schenley in Pittsburgh will be the headquarters for the Board, and formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for *re-examination* in Part II must make written application to the Secretary's Office not later than April 15, 1943.

The Pittsburgh Obstetrical and Gynecological Society will hold an informal subscription dinner meeting at the Hotel Schenley, on Saturday evening, May 22, 1943, at 7:00 P.M. Visitors, here for the examinations, are cordially invited to make arrangements to attend. Reservations may be made by writing to Dr. Joseph A. Hepp, Secretary of the Society, at 121 University Place, Pittsburgh, Pa. An interesting program is being provided.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1944 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

To Our Readers

The exigencies of the war situation have made it necessary to comply with the order of the War Production Board to reduce the weight of paper previously used for the JOURNAL. While this change will not affect the printed page it will affect the quality of the halftone illustrations. We regret that we have no choice in the matter and would ask the forbearance of our readers. As soon as the restrictions are removed, we shall resume our practice of printing the JOURNAL on the previously employed heavier grade of paper.

<div align="right">The C. V. Mosby Co., Publishers.</div>

Necrology

WILLIAM EDGAR CALDWELL, Professor of Clinical Obstetrics and Gynecology and Associate Director of the Sloane Hospital for Women, Columbia University, died at his home in New York City, on April 1, 1943, at the age of 63. He graduated from the New York University and Bellevue Hospital Medical School in 1904, and later served as Assistant Professor of Obstetrics, and in 1920 transferred to the Sloane Hospital with his former chief, Dr. Wm. E. Studdiford, who succeeded Dr. Edward B. Crugin, as Professor of Obstetrics at the College of Physicians and Surgeons and Director of the Sloane Hospital for Women.

Among the many contributions by Dr. Caldwell to the literature, his most recent and noteworthy ones deal with the roentgenology and classification of pelvic morphology.